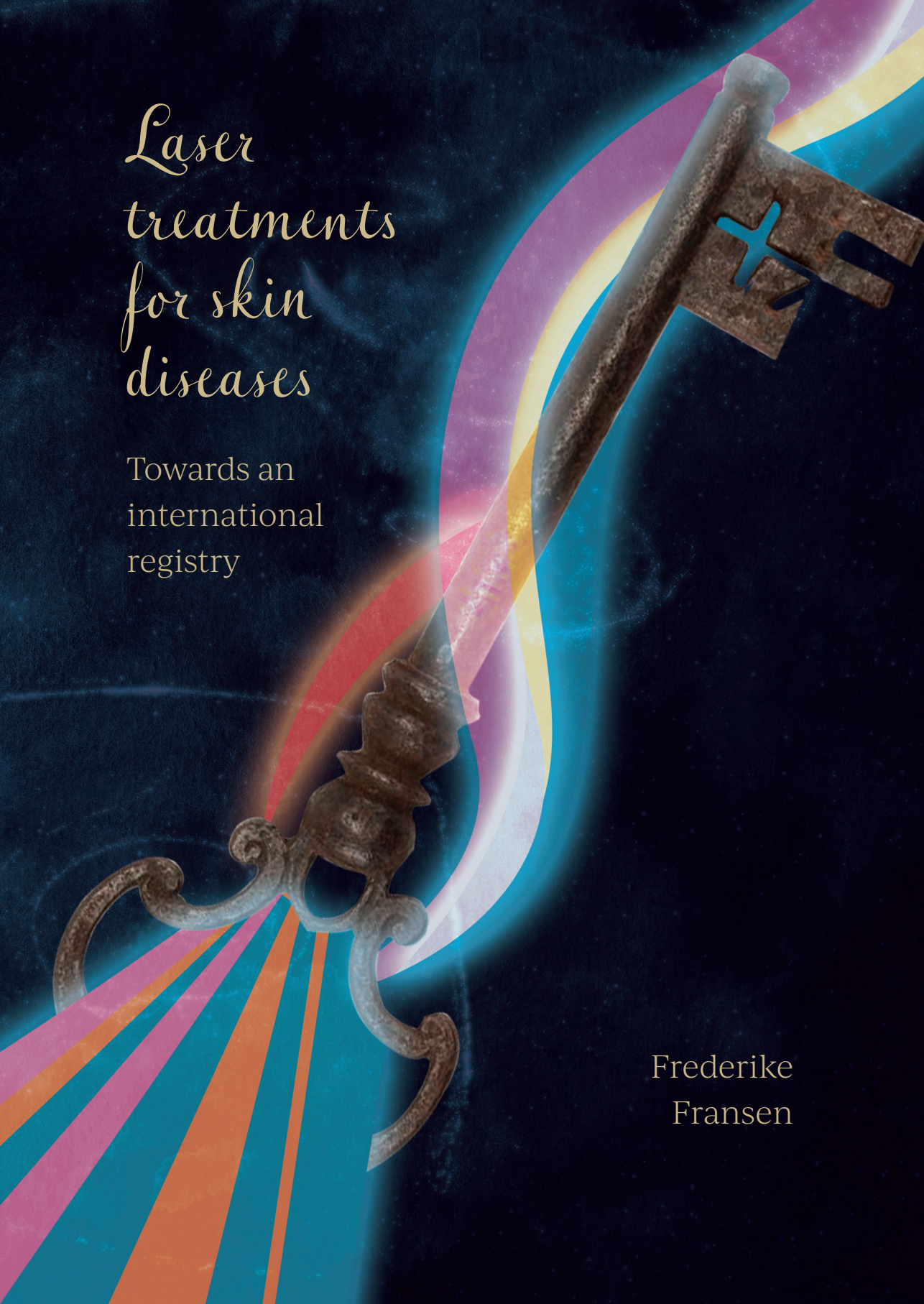
Laser treatments for skin diseases

Towards an international registry



Frederike Fransen

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Towards an international registry

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Laser treatments for skin diseases - Towards an international registry
PhD thesis, University of Amsterdam, Amsterdam, the Netherlands

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CHAPTER 1

General introduction and outline of the thesis

Use of lasers in dermatology

Over the years and with the progress of technology, laser therapy has become a rapidly evolving and exciting field in dermatology. Through selective photo-thermolysis, lasers revolutionized cosmetic dermatology and also promoted a safe and effective means for treating various medical indications. These devices found application in treatments for vascular lesions, pigmentary disorders, tattoo removal, hair follicle related diseases, skin neoplasms, inflammatory disorders and scars. (1) Many of these skin disorders meet the criteria of an orphan disease.

Laser therapy grasped the attention as it showed advantages in comparison to conventional surgical or radiotherapeutic treatments, that are often limited by their side effects, such as the risk of scarring of the skin. The progressing technology allowed to manipulate the properties of lasers and adapt them for even more specific use in their therapeutic purpose. This wide area of clinical use in dermatology was unimaginable just after the introduction of lasers in medicine. In fact, in the very beginning lasers were called "a solution looking for a problem". (1)

Laser types and Indications

The indications for laser therapy are often based on targeted absorption of the laser light by specific chromophores in the skin. There are indisputable indications for lasers nowadays that were made possible by manipulating the physical characteristics of lasers. (1) The current state of laser use with regard to the most important lasers and their therapeutic purpose in dermatology is shortly presented here.

1. Vascular lasers

Lasers are a good therapeutic tool for congenital and acquired vascular lesions. Since the 1980s, improved systems for vascular indications have been introduced. A vascular laser is a device that emits radiation that is strongly absorbed by the chromophores, oxy- and deoxyhemoglobin, which have absorption peaks at 418, 542 and 577 nm. (1-2) The radiant energy of the laser is preferentially absorbed by HbO2 within the vascular lesion and converted to heat which results in thermal damage and vessel thrombosis. Modern vascular lasers have the option of adapting the pulse duration to the type of vascular abnormality and using skin cooling systems during the laser treatment in the form of spray cooling, contact cooling or cold air cooling.(2)

A wide variety of vascular skin lesions are responsive to vascular laser therapy (table 1). Examples of indications are port wine stains, venous malformations, angiokeratomas, capillary hemangiomas, spider angiomas, facial telangiectasias, venous lakes, telangiectatic leg veins and poikiloderma of Civatte.(3-5)

2. Pigment lasers

A pigment laser is a device that targets chromophores of melanin or exogenous pigments (tattoo, drug pigmentation, iron). Melanin has a broad absorption spectrum and thus, yellow, green, red and near-infrared lasers can be used for this indication.(4) In addition, a pigment laser has a very short pulse duration that is adapted to the size of the pigment particles (melanosomes).(6) The classic pigment laser is the Q-switched ruby laser (694 nm). In addition, the Q-switched alexandrite laser (755 nm) and the Q-switched Nd:YAG laser (1064 nm, possibly 'frequency-doubled' 532 nm) are also used for the same indications.

Some pigmented dermatoses are more amenable to laser therapy than others. In addition to the Q-switched lasers operating in the nanosecond range, so-called picosecond lasers have also been used. The pulse duration of these lasers is roughly ten to hundred times shorter than the older Q-switched lasers, so that the pigment particles are crushed into even smaller grains. All these pigment lasers, have successfully been used for the treatment of epidermal pigmented lesions, such as lentigines and ephelides. However, some epidermal pigmented lesions may be resistant such as melasma, because of recurrence. Moreover, the ability of lasers like the NdYAG laser to penetrate 4-6 mm into human skin makes this treatment also effective for dermal pigmented lesions of nevi of Ito, Hori and Ota, and post inflammatory hyperpigmentation (PIH). (table 1) (6)

3. Ablative lasers

They are often referred to as surgical lasers or wounding lasers. The ablative laser is based on the principle that the laser radiation is absorbed by water, which accounts for more than 80% of the skin's composition, the water phase of tissue.(8) In ablative facial resurfacing a photoablative interaction takes place in which tissue evaporates. In case of rejuvenation treatments removing photodamaged areas of the epidermis is achieved and tissue healing stimulates collagen production.(4)

Ablative lasers capable of high peak powers with short pulse durations were required to achieve more precise tissue removal with limited thermal damage as compared to the older continuous wave surgical lasers. The unique characteristics of the surgical laser makes it a versatile surgical tool which can be used either for surgical incisions or volume ablation by vaporization of skin as utilized for indications such as laser resurfacing, acne scars, angiokeratoma, epidermal nevi, neurofibromas, xanthelasma, rhinophyma, syringoma and granuloma faciale (table 1).(5, 8)

Mainly two ablative laser systems are used in dermatology: the carbon dioxide (CO2) laser with a wavelength of 10,600 nm and the Erbium:Yttrium Aluminum Garnet (Er:YAG) laser with a wavelength of 2,940 nm.(9, 10)

During Er:YAG laser ablation, delivered radiation is highly absorbed by water, resulting in ablation with minor thermal injury to the surrounding skin tissue.(11)

Therefore, the results in terms of neocollagenesis after Er:YAG laser resurfacing are moderate in comparison with CO2 laser treatment, but it also makes it a safer method especially suitable for treating sensitive areas and mild to moderate rhytids and photodamaged skin. (4) Consequently, the Er:YAG laser is known for the minor thermal injury, fast reepithelization, fast resolution of post-treatment erythema, short downtime and few complications. (10, 11)

4. Fractional lasers

Fractional photothermolysis is a relatively new concept in laser dermatology and was published in 2004 by Manstein et al.(12) This technique can involve both ablative and non-ablative tissue effects. Ablative fractional resurfacing produces clinical and histologic changes comparable to ablative lasers, but spares most of the skin due to rapid reepithelization and mild side effects.(13, 14)

Instead of a broad laser beam, many (hundreds to thousands) narrow laser beams, usually 120-300 micrometers in diameter, are applied. This creates narrow, deep holes when an ablative wavelength is used or columns of necrosis when a non-ablative laser is used with intact tissue in between. Because narrow cylinders of damaged skin alternate with intact skin, the appearance of visible wounds is prevented, healing time is short and the risk of side effects is low. More than a hundred different fractional laser devices have been introduced so far to the market, using more than ten different wavelengths.(14, 15)

There are two main categories: the evaporative (ablative) and the non-evaporative (non-ablative) fractional lasers. Both types of fractional lasers are mainly used for cosmetic indications such as epidermal pigmentation, photoaging, melasma, rhytides, atrophic, surgical, and acne-related scarring and additional textural imperfections.(15, 16) (table 1) However, there are various skin disorder that have been reported to improve with fractional lasers although strong evidence is lacking.

An interesting development is laser-assisted drug delivery. The holes of the vaporizing fractional laser are used to increase the dermal delivery and thereby the bioavailability of drugs.(17)

5. Laser hair removal

In 1995, the FDA approved the first energy-based application designed for long-term hair reduction based on the principles of selective photothermolysis. Since that time, a multitude of lasers and light sources have been developed for this indication.(18) The target chromophore for laser hair removal is melanin.(19) The follicular structure responsible for regeneration has not been identified yet and current devices target the entire hair follicle.

There are three most important lasers used nowadays for hair removal. The alexandrite laser (755 nm) is the laser with the shortest wavelength for hair removal.

Due to the high absorption of light by melanin at this wavelength, the alexandrite laser is able to remove lightly pigmented hairs from light skin. It should be used with extreme caution in darker skin types due to possible hypopigmentation and post-inflammatory hyperpigmentation.(20) The diode laser (800 and 810 nm) can be used on all skin types, while the best results are achieved on darker hair. Diode lasers are the most commonly used laser for hair removal nowadays.(21) The Nd:YAG laser (1064nm) operates at a wavelength that is minimally absorbed by melanin, which makes this laser safe in persons with dark skin types for removal of dark, coarse hairs (table 1).(19, 22)

Table 1. Overview of most widely used indications for laser treatment in dermatology

Laser type	Widely used indications
Pigment specific lasers	*Epidermal pigmented lesions* solar lentigines, ephelides, café au lait macules and seborrheic keratoses *Dermal lesions* melanocytic nevi, blue nevi, drug induced hyperpigmentation, and nevus of Ota and Ito *Both an epidermal and dermal component* postinflammatory hyperpigmentation, melasma and nevus spilus *Other* Tattoo removal
Vascular lasers	port wine stain, hemangioma, facial telangiectasia, rosacea, spider angioma, pyogenic granuloma, spider angioma, poikiloderma of Civatte, pyogenic granuloma, venous lake, leg veins, cherry angioma, blue rubber bleb nevus syndrome, cutaneous lesions of Kaposi sarcoma.
Laser hair removal	removal of dark, coarse hair
Ablative laser	laser resurfacing, acne scars, angiokeratoma, epidermal nevus, seborrheic keratosis, actinic cheilitis, keloids, sebaceous hyperplasia, xanthelasma, skin tags, warts, neurofibromas, xanthelasma, rhinophyma, syringoma and granuloma faciale. photoaging, facial wrinkles, Surgical or traumatic scars
Fractional laser	epidermal pigmentation, photoaging, melasma, rhytides, atrophic, surgical, and acne-related scarring, textural imperfections.

Treatment options and plume hazards

Of utmost importance is the safety of both patients and physicians during laser treatment. Fundamental safety measures include education, eye and skin protection, as well as protection from plume hazards. The interaction between a heat producing device and the treated tissue has the potential to produce surgical smoke or plume. It is known that laser plume may harbor an infectious potential. Moreover, numerous

chemical substances, some carcinogenic, have been detected in the laser plume, such as carbon monoxide, hydrogen cyanide, ammonia, formaldehyde, acrolein, and benzene. (23) Although there are guidelines for respiratory protection at the workplace in many countries, these safety procedures are not generally adopted. (24, 25)

International Registry for Outcome Measurement

The continuous evolution of laser devices created therapeutic options for common and uncommon skin disorders and cosmetic purposes. (1) Due to all different laser devices on offer and their use for many different skin disorders, generally, the quality of evidence is low, consisting of a rather small body of randomized controlled trials and mostly of case series.

The current literature is insufficient to provide clinicians with guidance on appropriate indications and details of the optimal laser regimen. This lack of evidence results both in overtreatment (patients who receive ineffective laser treatments) and undertreatment (patients who do not receive potentially effective laser treatment).(26) Moreover, failure to pool research findings because of heterogenous outcomes, restrict the uptake of new evidence into practice.(27)

Generic Core Outcome Set

Recently, the initiative of the international "Laser trEAtments in Dermatology" (LEAD) registry has been launched to address some of these issues. The approach to develop and use a core outcome set (COS) in laser treatment research and clinical practices supports this endeavor. A COS is defined as an agreed standardized set of outcomes that should be measured and reported, as a minimum, in 3 settings of clinical trials, daily practice and registries of a specific disease.(28)

COS are currently being developed for a broad variety of skin diseases, such as eczema, hidradenitis suppurativa and vascular malformations.(29-31) They represent a minimum set of outcomes selected and agreed upon their relevance by key stakeholders, including health care professionals, researchers and patients. The Cochrane Skin Group – Core Outcome Set Initiative (CSG-COUSIN) is a research working group within the international Cochrane Skin Group which has the mission to develop and implement COSs in dermatology.(32) The key stakeholders need to decide by a consensus method, e.g., the Delphi procedure, which outcome domains are of importance, and select the outcome measurement instruments for each domain to develop a COS for the specific disease.(28, 32) However, with so many skin diseases involved, reaching consensus on core domains, core outcomes and measurement instruments for the purpose of the laser registry is challenging. Given this time-consuming process of selecting core domains and measurement instruments, it is impossible to reach consensus on a COS for each

skin condition apart. All the more as there are hundreds of uncommon dermatological conditions for which laser treatments have been published.

We, therefore, suggest to develop and use a 'generic' core outcome set (GOS) that, subsequently, will facilitate to pool data in the LEAD registry on multiple laser interventions for various skin disorders. Assuming that there are universally valid and relevant outcomes across various skin disorders, the development of a GOS is a starting point for use in the upcoming international laser registry.

Aims and outline of the thesis

This thesis is divided into two parts, covering outcome measurements for the international Laser trEAtments in Dermatology (LEAD) registry and clinical considerations for laser treatments. This is followed by a general discussion of the content of this thesis and future perspectives.

Part I: Development of the Generic Outcome Domain Set (GDS) for the international Laser trEAtments in Dermatology (LEAD) Registry

Chapter 2: A Generic Outcome Set for the international registry on Laser trEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on what to measure

Chapter 3: A Systematic Review of Outcome Reporting in Laser Treatments for Dermatological Diseases

Chapter 4: A Generic Outcome Domain Set for a registry on laser treatments in dermatology: a Delphi process and consensus meeting

In part I of this thesis we aim to identify heterogeneity in study outcomes in laser treatment research and to describe solutions to improve homogeneity in outcome reporting.

The second aim is to prepare and develop a Generic Outcome Set (GOS) for the international Laser trEAtments in Dermatology (LEAD) registry. The goal of the global study is to reach an international consensus on generic outcomes for the international laser registry. For the development of a GOS, a step-by-step approach needs to be undertaken which is described in a protocol **(chapter 2).** We followed the method of the CS-COUSIN organization which provides guidelines for the process of developing a Core Outcome Set and how it can be implemented in the field of dermatology. The first phase in developing a GOS is a literature review on the types of outcomes and outcome measures used in previously published literature on laser treatments in Dermatology

(chapter 3). The second phase in developing a GOS is an eDelphi study and a consensus meeting. In this process, the outcomes identified in the literature review are categorized into a questionnaire for healthcare professionals and a separate questionnaire for patients. Next, three sequential rounds of the questionnaire are presented to prioritize these outcomes. Phase three consists of an online consensus meeting with healthcare professionals to agree on the Generic Outcome Domains set (GDS) as part of the GOS. This eDelphi study is described in **chapter 4.**

Part II: Laser Treatments and Safety in Clinical Practice

Chapter 5: Laser treatment of epidermal nevi: A multicenter retrospective study with long-term follow-up

Chapter 6: Ultrafine particle concentrations during laser hair removal: Effectiveness of smoke evacuators

Chapter 7: Laser-induced smoke in dermatologic practice: A survey to explore hazard perceptions, safety measures and unmet needs

In part II we examine long-term outcomes of laser treatment of epidermal nevi. (**chapter 5**). Furthermore, we focus on laser-induced smoke as a potential health hazard to exposed physicians and the effectiveness of safety management. First, we investigated the effect of different laser devices and different smoke evacuators on the ultrafine particle concentrations in the room during laser hair removal (**chapter 6**). Second, we assessed the actual use of safety measures and explored the current perceptions of health hazards of laser-induced smoke and smoke management among members of the European Society for Lasers and Energy Based Devices (ESLD) **(chapter 7).** The findings presented in this thesis are discussed in **chapter 8** together with future perspectives on the research topics.

References

1. Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology: four decades of progress. J Am Acad Dermatol. 2003;49(1):1-31; quiz -4.
2. Dai T, Diagaradjane P, Yaseen MA, Pikkula BM, Thomsen S, Anvari B. Laser-induced thermal injury to dermal blood vessels: analysis of wavelength (585 nm vs. 595 nm), cryogen spray cooling, and wound healing effects. Lasers Surg Med. 2005;37(3):210-8.
3. Adamic M, Troilius A, Adatto M, Drosner M, Dahmane R. Vascular lasers and IPLS: guidelines for care from the European Society for Laser Dermatology (ESLD). J Cosmet Laser Ther. 2007;9(2):113-24.
4. Alster TS, Lupton JR. Lasers in Dermatology. American Journal of Clinical Dermatology. 2001;2(5):291-303.
5. Gianfaldoni S, Tchernev G, Wollina U, Fioranelli M, Roccia MG, Gianfaldoni R, et al. An Overview of Laser in Dermatology: The Past, the Present and ... the Future (?). Open Access Maced J Med Sci. 2017;5(4):526-30.
6. Stratigos AJ, Dover JS, Arndt KA. Laser Treatment of Pigmented Lesions-2000: How Far Have We Gone? Archives of Dermatology. 2000;136(7):915-21.
7. Zhong Y, Yang B, Huang L, Elias PM, Man MQ. Lasers for Becker's nevus. Lasers Med Sci. 2019;34(6):1071-9.
8. Conforti C, Vezzoni R, Giuffrida R, Fai A, Fadda S, Marangi GF, et al. An overview on the role of CO2 laser in general dermatology. Dermatologic Therapy. 2021;34(2):e14692.
9. Riggs K, Keller M, Humphreys TR. Ablative laser resurfacing: high-energy pulsed carbon dioxide and erbium: yttrium-aluminum-garnet. Clinics in dermatology. 2007;25(5):462-73.
10. Štulhofer Buzina D, Lipozenčić J, Bukvić Mokos Z, Čeović R, Kostović K. Ablative laser resurfacing: is it still the gold standard for facial rejuvenation? Acta Dermatovenerologica Croatica. 2010;18(3):0-.
11. Agrawal N, Smith G, Heffelfinger R. Ablative skin resurfacing. Facial Plastic Surgery. 2014;30(01):055-61.
12. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery. 2004;34(5):426-38.
13. DeBruler DM, Blackstone BN, Baumann ME, McFarland KL, Wulff BC, Wilgus TA, et al. Inflammatory responses, matrix remodeling, and re-epithelialization after fractional CO2 laser treatment of scars. Lasers in Surgery and Medicine. 2017;49(7):675-85.
14. Omi T, Numano K. The role of the CO2 laser and fractional CO2 laser in dermatology. Laser therapy. 2014;23(1):49-60.
15. Paasch U. The future of fractional lasers. Facial Plastic Surgery. 2016;32(03):261-8.
16. Preissig J, Hamilton K, Markus R. Current Laser Resurfacing Technologies: A Review that Delves Beneath the Surface. Semin Plast Surg. 2012;26(3):109-16.
17. Hædersdal M, Sakamoto FH, Farinelli WA, Doukas AG, Tam J, Anderson RR. Fractional CO2 laser-assisted drug delivery. Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery. 2010;42(2):113-22.
18. Gan SD, Graber EM. Laser hair removal: a review. Dermatologic Surgery. 2013;39(6):823-38.

19. Dierickx CC. Hair removal by lasers and intense pulsed light sources. Dermatol Clin. 2002;20(1):135-46.

20. Ash K, Lord J, Newman J, McDaniel DH. Hair removal using a long-pulsed alexandrite laser. Dermatol Clin. 1999;17(2):387-99, ix.

21. Goldberg DJ. One-year follow-up results of hair removal using an 810 nm diode laser. J Cosmet Dermatol. 2018;17(5):775-8.

22. Littler CM. Hair removal using an Nd:YAG laser system. Dermatol Clin. 1999;17(2):401-30, x.

23. Barrett WL, Garber SM. Surgical smoke: a review of the literature. Is this just a lot of hot air? Surg Endosc. 2003;17(6):979-87.

24. Searle T, Ali FR, Al-Niaimi F. Surgical plume in dermatology: an insidious and often overlooked hazard. Clin Exp Dermatol. 2020;45(7):841-7.

25. Dudelzak J, Goldberg DJ. Laser safety. Curr Probl Dermatol. 2011;42:35-9.

26. Kearney M, Treadwell J, Marshall M. Overtreatment and undertreatment: time to challenge our thinking. Br J Gen Pract. 2017;67(663):442-3.

27. Clarke M, Williamson PR. Core outcome sets and systematic reviews. Syst Rev. 2016;5:11.

28. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13:132.

29. Thorlacius L, Ingram JR, Garg A, Villumsen B, Esmann S, Kirby JS, et al. Protocol for the development of a core domain set for hidradenitis suppurativa trial outcomes. BMJ Open. 2017;7(2):e014733.

30. Gerbens LAA, Apfelbacher CJ, Irvine AD, Barbarot S, de Booij RJ, Boyce AE, et al. TREatment of ATopic eczema (TREAT) Registry Taskforce: an international Delphi exercise to identify a core set of domains and domain items for national atopic eczema photo- and systemic therapy registries. Br J Dermatol. 2019;180(4):790-801.

31. Langbroek GB, Wolkerstorfer A, Horbach SER, Spuls PI, Kelly KM, Robertson SJ, et al. Development of a core outcome domain set for clinical research on capillary malformations (the COSCAM project). J Eur Acad Dermatol Venereol. 2021;35(9):1888-95.

32. Kottner J, Jacobi L, Hahnel E, Alam M, Balzer K, Beeckman D, et al. Core outcome sets in dermatology: report from the second meeting of the International Cochrane Skin Group Core Outcome Set Initiative. Br J Dermatol. 2018;178(4):e279-e85.

PART I

Development of the Generic Outcome Domains Set (GDS) for the international Laser trEAtments in Dermatology (LEAD) Registry

CHAPTER 2

A generic outcome set for the international registry on Laser TrEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on *what* to measure

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Abstract

Introduction: While laser technology has expanded the armamentarium of treatment for various skin diseases during the past years, heterogeneity in study outcomes hampers comparability and appropriate evidence synthesis. Part of these issues can be addressed by developing a generic outcome set. Using the Delphi method, this study aims to seek consensus between key stakeholders on relevant generic outcomes (*what* to measure) for implementation in the international registry on Laser trEAtments in Dermatology (LEAD). The registry is focused on collecting research data on various laser treatments for skin disorders.

Methods and analysis: By reviewing the literature and involvement of key stakeholder groups and adult patients in need or after laser surgery and health professionals, a preliminary list of outcomes will be generated and categorized into domains. Using these outcomes, an international three-round Delphi study will be performed to rate the importance of outcomes in the selection of a generic outcome set. Participants are allowed to provide new outcomes to the prelimary list for revisions during the first Delphi round. Finally, results will be discussed during a consensus meeting to agree on generic outcomes to be used in the LEAD Registry.

Ethics and Dissemination: An ethics approval was not applicable (W19_290 # 18.336). The study is registered with the CS-COUSIN (Cochrane Skin Core OUtcome Set INitiative) and the Core Outcome Measures in Effectiveness Trials (COMET) initiative. Procedures will be conducted according to the Declaration of Helsinki. The findings will be disseminated through peer-reviewed publications and conference presentations.

Article Summary

Strengths and limitations of this study

- This protocol outlines the first international consensus effort to develop a generic outcome set for use in the international LEAD laser registry.
- With advances in laser technology, considering outcomes of importance (*what* to measure) to patients and health professionals is crucial.
- A comprehensive systematic review will explore which outcomes are used and reported in existing studies on laser treatments.
- The Delphi procedure requires three survey rounds and involves a large group of stakeholders across various disciplines and geographical areas including patients, reflecting different viewpoints.

Introduction

During the past decades, modifications in laser technology have further widened its scope and greatly expanded the cutaneous laser surgeon's armamentarium [1,2]. Today, there are many medical indications in dermatology, encompassing vascular, pigmented, inflammatory, metabolic or infectious lesions, benign tumors, scars, and hair follicle-related skin conditions that are regularly - and sometimes exclusively - treated with lasers [1–3]. Many of these disorders meet the criteria of an orphan disease.

The diversity in laser devices and the spectrum of medical indications pose unique research challenges for clinical decision-making in laser therapy. Because most laser physicians are not exposed to large numbers of patients receiving laser treatments for uncommon indications, knowledge on the most effective laser treatment, including safety and used regimen, is unclear. The current evidence for most of these specific skin conditions is sporadic at best, consisting mostly of case reports and case series and only a very small number of randomized controlled trials (RCTs) [4,5]. Moreover, most often only isolated successes are reported while cases that failed to respond are not published, leading to publication bias [6].

Another issue hampering evidence synthesis is heterogeneity of outcome definition, measurement and reporting in laser research. Patient-reported outcomes (PROs), such as 'patient experience of laser treatments' and 'health-related quality of life', are often not reported and together with selective outcome reporting in laser research, it is all a serious threat to comparative effectiveness research as it limits the ability to compare, contrast, and combine individual studies [7,8]. As a result, this hampers to draw meaningful conclusions and guidance to inform clinical decision-making [9,10].

To overcome this issue in the field of laser dermatology, the development of the International Laser Treatment (LEAD) Registry has been proposed to initiate collaborative data pooling of a wide range of skin disorders. The development of a registry may be the key to the lack of solid evidence for laser treatments in dermatology, however, well-defined standardized and generic outcomes are required for its establishment.

To address the variations in outcome reporting, organizations such as the Core Outcome Measures in Effectiveness Trials Initiative (COMET) bring together researchers interested in developing a standardized set of core outcomes in various health-related fields [11]. A core outcome set (COS) is defined as an agreed minimum set of outcomes that should be measured and reported in all clinical trials for a specific health condition, including methods used to measure these core outcomes[10,12]. Throughout this report, the definition of "outcome" refers to a single construct that can be measured as a standalone item (e.g. 'erythema'), while the term "outcome domain" or "domain" is an umbrella term for a group of associated outcomes (e.g. 'signs as assessed by physician'). Furthermore, the outcome instrument refers to how the outcomes are measured.

Although a COS is recommended for clinical trials, they can also be developed for routine clinical practice, and for registries [10,12]. In 2015, the international, multidisciplinary working group, the Cochrane Skin Group- Core OUtcome Set INitiative (CS-COUSIN) has been established [13]. The organization supports dermatology-specific initiatives to develop and implement a COS by building upon experiences of the Harmonizing Outcome Measures for Eczema (HOME) initiative, which developed a roadmap to guide the process of COS development and implementation [14]. Currently, 17 COS initiatives have been supported by CS-COUSIN in dermatology. These projects involve 26 different skin diseases, such as acne, atopic eczema, hidradenitis suppurativa, melanoma, nail psoriasis, rosacea, and vitiligo [11,15]. However, with hundreds of different and mostly unrelated dermatoses that are treated with lasers in the field of laser dermatology, the need for a generic outcome set (GOS) is commanding. Therefore, we focus on developing a GOS (*what* to measure) for the purpose of the LEAD registry. The GOS is intended to be applied for the assessment of various, unrelated skin diseases that are treated with different types of lasers.

In summary, there is an urgency of using the same generic outcomes in laser therapy. Hence, establishing consensus on the relevant outcomes for the LEAD registry will promote clinical researchers to use outcomes chosen by consensus that are relevant to patients and clinicians. The use of generic outcomes support data synthesis for many diseases in dermatology. The protocol outlines the context, scope and methods for the development of a GOS to be implemented in the LEAD registry.

Aims and objectives

Aim

The aim of this study is to reach consensus between various stakeholders on generic outcomes relevant for the LEAD registry.

Objectives

Our study objectives are:

1. To identify outcomes that have previously been used and reported in RCTs, cohort studies, case-control studies and case series from a literature review and classify these outcomes into domains according to the COMET taxonomy;
2. To reach consensus between stakeholders on the outcomes of a GOS to be implemented in the LEAD registry.

Scope and applicability of outcomes

The registry is envisioned to suit all types of laser interventions for skin disorders in dermatology including vascular, pigmented or inflammatory lesions, benign tumors, scars, and hair follicle-related skin conditions treated with lasers. The GOS is intended for use in the LEAD registry, with the focus on prospectively recording the effectiveness and safety of cutaneous non cosmetic laser interventions. Therefore, we excluded laser assisted drug delivery, low laser level therapy, body- contouring, skin tightening, hair removal, rejuvenation and anti-aging procedures. Furthermore, because of the distinctive mode of action and use in daily clinical practice, laser assisted drug delivery, low laser level therapy and laser procedures for (leg) veins were excluded.

Methods

Research group

The steering committee (FF, PS, AW, MA, AB, PB, IH, MH, LH, KK, TK, HL, WM, LM, KN, UP, TP, CP, IV) provide input at critical points of the study such as protocol development, stakeholder recruitment, consensus process and the consensus meeting. Three members of the steering committee (FF, PS, AW) coordinate the overall project, ensure methodological quality of the project and make key decisions. All members of the steering committee will participate in the Delphi procedure as well as in the final consensus meeting. The steering committee has representatives from The Netherlands, Denmark, Egypt, France, Germany, Israel, Italy, Japan, Spain, Switzerland, Thailand and USA, with extensive expertise in various laser treatments, outcomes research and clinical research.

Study design

Figure 1 provides a brief overview of the stepwise approach with different research methods. The study consists of the following two phases:

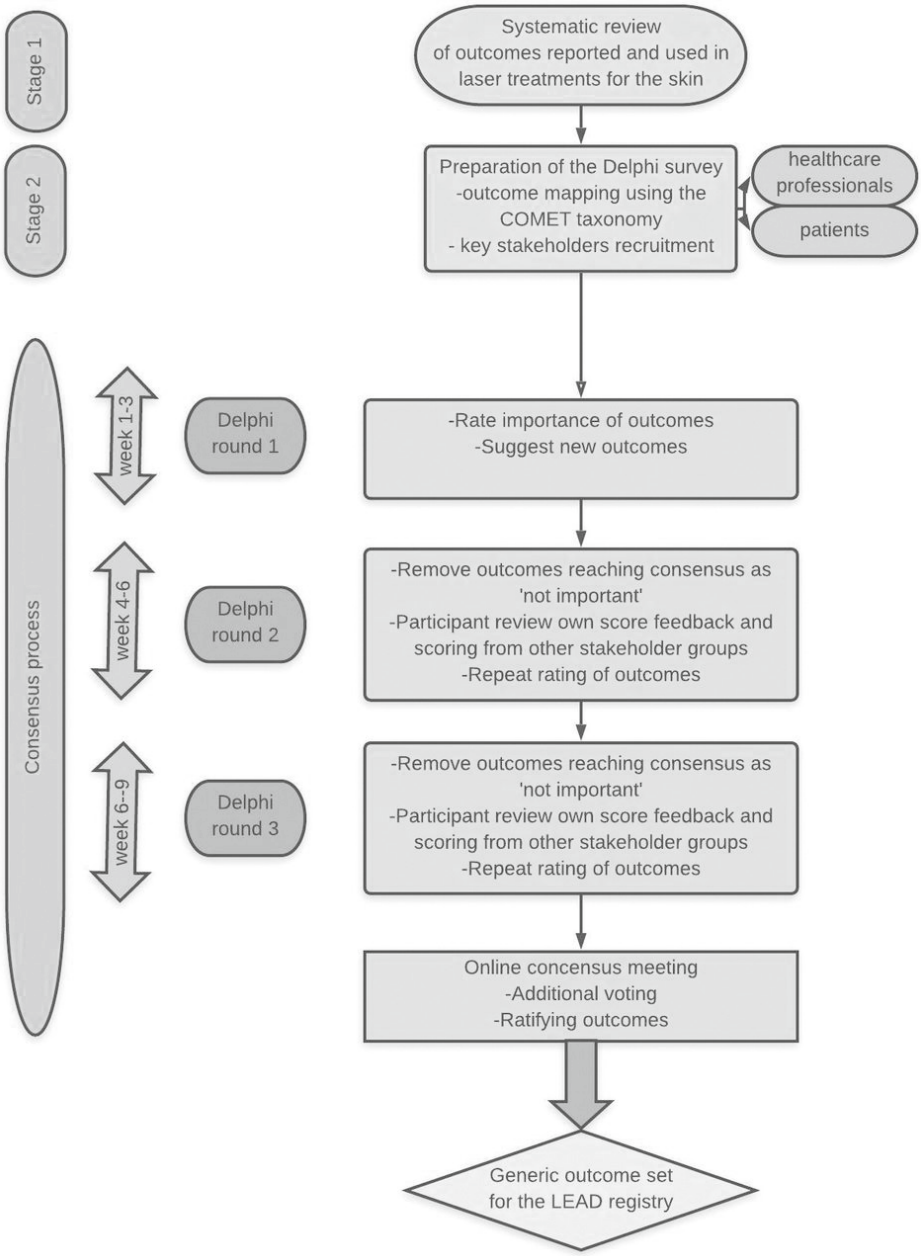

Figure 1. Flow diagram outlining the development of a generic outcome set for the Laser trEAtments in Dermatology (LEAD) registry. Preparatory stages and process of consensus for relevant generic outcomes are summarized. COMET, Core Outcome Measures in Effectiveness Trials Initiative.

Phase 1: Identification of potential outcomes important in laser treatments by means of a
1. A systematic review to form the preliminary list of outcomes for the Delphi survey
2. Classification of outcomes into domains according to the COMET taxonomy [19]

Phase 2: A consensus process involving key stakeholders who are able to suggest additional outcomes during the first round and who will rate the importance of outcome for reaching consensus on the GOS by means of a
1. Three-round Delphi survey.
2. Expert consensus meeting. attended by representatives of all stakeholder groups.

This study is registered with the CS-COUSIN and COMET initiative [11,16]. Results of the consensus study will be reported according to the Core Outcome Set-STAndards for Reporting (COS-STAR) [17].

Phase 1: Identification of potential outcomes and domains

Phase 1.1: Systematic literature review

The first phase of the study is to identify which outcomes should be measured and reported in a registry on laser treatments for skin disorders (what to measure: the GOS, see definitions in supplementary file 1). A SR will be performed to explore existing outcomes that are used in laser studies. According to the COMET guidelines [18], searches will be performed in the following database: MEDLINE and EMBASE. Articles between January 2013 and December 2017 will be retrieved. A recent 5-year time period has been selected for the search so that outcomes extracted represent the practice of present-day laser research. The inclusion and exclusion criteria are presented in Table 1. Two reviewers will select articles and extract the data independently. Disagreement will be resolved by discussion and by consulting a third review author if necessary. The following data will be extracted from the selected articles in data extraction tables: authors, years of publication, country, cutaneous indications for treatment and type of laser treatments. We will assess what outcomes and outcome measurement instrument are used, consistency in outcomes, number of times an outcome was used, consistency in classification used.

Table 1. Inclusion and exclusion criteria for literature review

	Inclusion criteria	Exclusion criteria
Patient population and indication	Studies including patients age 18 and older with vascular, pigmented, inflammatory, metabolic or infectious lesions, benign tumours and hair follicle-related skin conditions treated with lasers	Non-humans flebological skin conditions Laser assisted drug delivery, low laser level therapy, body-contouring, skin tightening, hair removal, rejuvenation and anti-aging
Study design	RCTs, cohort studies, case-control studies, case series	In vitro studies, systematic reviews, abstracts and expert opinions, case reports
Intervention	Any type of laser treatment for vascular, pigmented or inflammatory lesions, benign tumours, and hair follicle-related skin conditions.	Laser assisted drug delivery, low laser level therapy, laser therapy for leg veins and cosmetic interventions (see scope of outcomes)
Outcomes		Non-clinical outcomes e.g. biochemical outcomes, imaging, confocal laser, histology
Publication	All studies are conducted between 2013-2017	

Phase 1.2: Classification of outcomes into domains

Subsequently, data will be classified according to the standardized taxonomy for outcomes proposed by the COMET initiative [19]. This taxonomy encompasses 38 domains within 5 core areas: mortality/survival; physiological/clinical; life impact; resource use; adverse events.

Outcomes and their classification in domains will be discussed with three members (FF, PS, AW) of the steering committee. The preliminary list of outcomes classified to domains will be included in the consensus process.

Phase 2: Consensus process

Phase 2.1: Delphi procedure

For investigating crucial outcomes in context of the LEAD registry, a Delphi study will be conducted. The Delphi is based on a structured process for gathering and condensing knowledge from key stakeholder groups by means of 3 rounds with a series of questionnaires [20]. The procedure will consist of three online rounds (Figure 1).

Participants

The involvement of a variety of stakeholders is a key part for the identification of outcomes and strongly recommended by methodologists [21].

The following representatives from four international key stakeholder groups are involved in the process of reaching consensus on outcomes:

1. Patients of age 18 with vascular, pigmented, inflammatory, metabolic or infectious lesions, benign tumours and hair follicle-related skin conditions treated by lasers.
2. Patient representatives involved in patient associations that raise awareness on the impact of vascular, pigmented, inflammatory, metabolic or infectious lesions, benign tumours and hair follicle-related skin conditions.
3. Health care professionals – Laser experts who treat patients with vascular, pigmented or inflammatory, metabolic or infectious lesions, benign tumours, hair follicle-related skin conditions and who are involved in research on laser treatments.
4. Health care professionals –General physicians who treat patients with dermatological indications.

Panel size and recruitment

There is no robust guidance for calculating the number of participants needed for a Delphi study and expectations are based on COMET Initiative guidelines and previous literature [16,22,23]. As there are various stakeholder groups involved in the Delphi procedure, we will recruit as many international representatives as possible from each group. All potential participants will be invited with a letter explaining the aims and details of the study and the rationale and importance of completing the entire Delphi process. Respondents who agree to take part will be assigned a unique identification number. Furthermore, each member of the steering committee will be asked to cascade the link of the survey to 3 other physicians in their network. Patients and patient representatives will be recruited from national and international support groups for skin diseases treated with lasers and can be found in supplemental file 2**.** In addition, laser experts from the steering committee will be asked to recruit 3 patients with different skin conditions treated with lasers in their center. To make sure that we involve skin diseases of different categories, laser experts will indicate the diagnosis of the patients that are recruited. By sending the survey invitation to experts and patient support groups from different continents, we aim to reflect a broad range of patients and health professionals with diverse backgrounds and experiences. For each round, the number of participants invited and those who completed the surveys will be documented. The participants will have 3 weeks to complete each round. We will send personal reminder emails to those who did not respond after 7 and 14 days to increase the response rate.

Delphi survey

Participants will be divided into a group of patients and a group of health professional, leading to separate scoring of outcomes. All participants will be asked to rate the importance of each of the outcomes using the GRADE (Grading of Recommendations Assessment, Development and Evaluations) approach. The scale will range from 1 to 9 and will be categorized as follows: 1–3 'not important'; 4–6 'important but not critical'; and 7–9 'critical' [24,25]. If participants feel unable to rate or provide feedback they can select 'unable to score'.

Delphi rounds

Delphi round 1

During the first round of the Delphi survey, baseline characteristics (age, gender, country of practice) will be obtained from all participants. Patients will be asked for their medical indication and type of laser treatment, and whether any complications have occurred during treatment. Health professionals will be asked their specialty (laser dermatology, general dermatology or other), workplace (academic, teaching hospital or non-teaching hospital) and years in practice. Next, participants will be asked to score listed outcomes and will have the option to suggest any additional outcomes that are not yet presented in the preliminary list.

Delphi round 2 and 3

In the second and third Delphi rounds, all participants will receive feedback on the scores of the previous round in both the patient and the health professional group. The outcomes from the previous rounds will be presented with the median scores from each stakeholder group combined with a histogram showing the scoring distribution. Subsequently, participants will be asked to score all outcomes for which consensus has not been reached, in the same manner as in the first Delphi round. Outcomes for which there was only consensus within a single stakeholder group will also be shown to the other stakeholder group to evaluate whether consensus can be achieved in both stakeholder groups**.**

Definition of consensus

The definition of consensus is presented in Table 2. 'Consensus in' is defined as approval of the outcome by the vast majority (70 %) of all stakeholder groups that score 7, 8, or 9 with fewer than the minority (15 %) of panelists scoring 1–3. On the contrary, 'consensus out' is defined as 70% or more of all stakeholder groups scoring as 1 to 3 and less than 15% scoring as 7 to 9 [12]. After three e-Delphi rounds, outcomes will be classified as 'consensus in' (consensus on the importance of the outcome), 'consensus out'

(no consensus on the importance, or consensus on non importance) or 'no consensus' (consensus on the importance in only one or or no consensus).

Table 2. Definitions of consensus for identifying generic outcomes for the LEAD registry

Consensus category	Clarification	Definition
Consensus in	Outcome should be included in the registry	70% of stakeholder groups scoring as 7 to 9 and < 15% of stakeholder groups scoring as 1 to 3
Consensus out	Outcome should not be included in the registry	70% or more of stakeholder groups scoring as 1 to 3 and < 15% of stakeholder groups scoring as 7 to 9
No consensus	Hesitation about relevance of outcome to be included in the registry	Anything other

Phase 2.2: Determination of the GOS during the expert consensus meeting

In case complete consensus is reached in the Delphi procedure on the outcomes of the GOS , no formal consensus meeting will be organized. However, the results of the Delphi will be discussed with three members of the steering committee (FF. PS, AW) to check misconceptions in the Delphi method and to safeguard a well-defined GOS. For outcomes for which consensus definition during the Delphi has not been reached, we invite 15 participants from across all stakeholder groups to participate in an online expert consensus meeting within 2 months after the close of round 3. The primary goal of the meeting is discussing the 'no consensus' outcomes. Consensus results from the Delphi can be reversed in this meeting if reasons are very strong and clear.

Patient and public involvement

Patient and public were not involved in the development of this study protocol. However, patients will be involved and included within the Delphi procedure as expert group. Consensus methodology will ensure that the opinions and preferences of patients will be given the same weighting as those of the laser experts and health professionals. Furthermore, patients will participate in the final consensus meeting. We disseminate the main results to study participants and patients by email which will include a copy of the final outcomes of the GOS. In addition, where approval has been given, participants (including members of the public) will be named as contributors in the acknowledgments section.

Discussion

By the end of this study, we hope to reach consensus on a GOS that could be implemented in an international registry with a research focus, that collects data of rare skin diseases treated by lasers. Analysis of registry data provides insight into effectiveness and safety of different laser treatments across many skin diseases, laser centers and countries.

There are several strengths using the Delphi method for this study. First, the Delphi method allows to recruit a large number of laser experts, physicians and patients from diverse regions globally. The diversity in the experts' backgrounds and expertise ensures maximum impact of the results. Secondly, the Delphi method is the accurate tool in consensus processes in various stakeholder groups as individuals are able to express their own opinions and feedback can be provided in a controlled anonymous way. This means that there is room for individual disagreement but also consideration of the answers given by other individuals and stakeholder groups as a whole. However, there are also limitations of the Delphi method. Results are dependent upon the composition of the participants. There is a risk of relative uneven representations among patients, but also health professionals. Especially, when focusing on a specific group of rare skin diseases, selection bias could result in insufficient representation of other skin disorders. We request health professionals of the steering committee to recruit patients with 3 different skin disorders. Through this method, we hope to ensure that all subgroups including vascular, pigmented, metabolic, inflammatory lesions, benign tumours and hair follicle-related skin conditions, will be adequately involved. For patients it might be a barrier to imagine what is important to be included in a registry for a broad range of diseases, rather than one disease that is important to themselves. We will stress the importance of agreeing on a GOS for all diseases in each round of the Delphi survey and consensus meetings. Photographs will be included to illustrate the variety of skin disorders that are involved. To provide the highest possible input we will extend our invitation to take part in the Delphi survey to patients and health professionals in Africa, Asia, South-America, Australia, in addition to Europe and North-America. With support from all panel members, we hope to ensure that the LEAD registry will be internationally relevant, accepted and ready to use.

Ethics and dissemination

The medical research ethics committee of the Academic Medical Center Amsterdam confirmed that the Dutch Medical Research Involving Human Subjects Act does not apply to this study (W19_290 # 18.336) and that complete approval of this study by the committee is not necessary**.** All participants involved in the Delphi study will be asked for their consent before taking part. All procedures will be conducted according to the Declaration of Helsinki. All results from the consensus study will be reported in peer-

reviewed indexed journals. The data will be presented at conferences chosen to reach a wide range of knowledge users.

Abbreviations

COMET: Core Outcome Measures for Effectiveness Trials; GOS: Generic Outcome Set; CSG-COUSIN: Cochrane Skin Group—Core Outcome Set Initiative; COSMIN: COnsensus-based Standards for the selection of health Measurement Instruments; GOS: Generic Outcome Set; GRADE: Grading of Recommendations Assessment; LEAD registry: Laser TrEAtment Dermatology registry; RCT: Randomized controlled trial.

Contributors

FF initiated the protocol, designed the study, wrote the manuscript and reviewed it for important intellectual content. PS contributed significantly to the study design and reviewed the manuscript for important intellectual content. CP contributed to the study design and reviewed the manuscript for important intellectual content. AW initiated the protocol, designed the study and reviewed it for important intellectual content. All authors (FF, PS, AW, MA, AB, PB, IH, MH, LH, KK, TK, HL, WM, LM, KN, UP, TP, CP, IV) read and approved the final manuscript.

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References

1 Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology: Four decades of progress. J. Am. Acad. Dermatol. 2003;**49**:1–31. doi:10.1067/mjd.2003.582

2 Husain Z, Alster TS. The role of lasers and intense pulsed light technology in dermatology. Clin. Cosmet. Investig. Dermatol. 2016;**9**:29–40. doi:10.2147/CCID.S69106

3 Houk LD, Humphreys T. Masers to magic bullets: an updated history of lasers in dermatology. *Clin Dermatol* 2007;**25**:434–42. doi:10.1016/j.clindermatol.2007.05.004

4 U.S. National Institutes of Health. ClinicalTrials.gov. clinicaltrials.gov. 2013.http://clinicaltrials.gov/ (accessed 28 Mar 2018).

5 Fransen F, Tio D, Prinsen CAC, *et al.* A Systematic Review of Outcome Reporting in Laser Treatments for Dermatological Diseases. *J Eur Acad Dermatology Venereol* Published Online First: 2019. doi:10.1111/jdv.15928

6 Atakpo P, Vassar M. Publication bias in dermatology systematic reviews and meta-analyses. *J Dermatol Sci* Published Online First: 2016. doi:10.1016/j.jdermsci.2016.02.005

7 Snyder CF, Aaronson NK, Choucair AK, *et al.* Implementing patient-reported outcomes assessment in clinical practice: A review of the options and considerations. Qual. Life Res. 2012. doi:10.1007/s11136-011-0054-x

8 Prinsen CAC, Mokkink LB, Bouter LM, *et al.* COSMIN guideline for systematic reviews of patient-reported outcome measures. *Qual Life Res* Published Online First: 2018. doi:10.1007/s11136-018-1798-3

9 Kirkham JJ, Gorst S, Altman DG, *et al.* COS-STAR: A reporting guideline for studies developing core outcome sets (protocol). *Trials* 2015;**16**. doi:10.1186/s13063-015-0913-9

10 Clarke M. Standardising outcomes for clinical trials and systematic reviews. Trials. 2007;**8**. doi:10.1186/1745-6215-8-39

11 http://www.comet-initiative.org/

12 Williamson PR, Altman DG, Blazeby JM, *et al.* Developing core outcome sets for clinical trials: Issues to consider. *Trials* Published Online First: 2012. doi:10.1186/1745-6215-13-132

13 Schmitt J, Deckert S, Alam M, *et al.* Report from the kick-off meeting of the Cochrane Skin Group Core Outcome Set Initiative (CSG-COUSIN). In: *British Journal of Dermatology*. 2016. 287–95. doi:10.1111/bjd.14337

14 Schmitt J, Apfelbacher C, Spuls PI, *et al.* The Harmonizing Outcome Measures for Eczema (HOME) Roadmap: A Methodological Framework to Develop Core Sets of Outcome Measurements in Dermatology. *J Invest Dermatol* Published Online First: 2015. doi:10.1038/jid.2014.320

15 Prinsen CAC, Spuls PI, Kottner J, *et al.* Navigating the landscape of core outcome set development in dermatology. *J Am Acad Dermatol* Published Online First: 2019. doi:10.1016/j.jaad.2019.03.009

16 Williamson P. The comet initiative. *Trials* 2013;**0**:68DUMMY.http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed13&AN=71799862%5Cnhttp://oxfordsfx.hosted.exlibrisgroup.com/oxford?sid=OVID:embase&id=pmid:&id=doi:&issn=1745-6215&isbn=&volume=14&issue=&spage=68DUMMY&pages=68DUMMY&date=2013&title= 17Kirkham JJ, Gorst S, Altman DG, *et al.* Core Outcome Set–STAndards for Reporting: The COS-STAR Statement. *PLoS Med* 2016;**13**. doi:10.1371/journal.pmed.1002148

18 Prinsen CAC, Vohra S, Rose MR, *et al.* Core Outcome Measures in Effectiveness Trials (COMET) initiative: Protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. *Trials* 2014;**15**. doi:10.1186/1745-6215-15-247

19 Dodd S, Clarke M, Becker L, *et al.* A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. *J Clin Epidemiol* 2018;**96**:84–92. doi:10.1016/j.jclinepi.2017.12.020

20 Jones J, Hunter D. Consensus methods for medical and health services research. *Br Med J* Published Online First: 1995. doi:10.2164/jandrol.111.015065

21 Harman NL, Bruce IA, Kirkham JJ, *et al.* The importance of integration of stakeholder views in core outcome set development: Otitis Media with Effusion in children with cleft palate. *PLoS One* Published Online First: 2015. doi:10.1371/journal.pone.0129514

22 Young A, Brookes S, Rumsey N, *et al.* Agreement on what to measure in randomised controlled trials in burn care: Study protocol for the development of a core outcome set. *BMJ Open* 2017;**7**. doi:10.1136/bmjopen-2017-017267

23 Schlessinger DI, Iyengar S, Yanes AF, *et al.* Development of a core outcome set for clinical trials in squamous cell carcinoma: Study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials* 2017;**18**. doi:10.1186/s13063-017-2069-2

24 Balshem H, Helfand M, Schünemann HJ, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* Published Online First: 2011. doi:10.1016/j.jclinepi.2010.07.015

25 The Grading of Recommendations Assessment Development and Evaluation. GRADE working group. *Grade* 2014.

SUPPLEMENTARY FILE 1

The definitions for COS, outcome, outcome instruments and outcome parameters according to Prinsen *et al*. (2014). [1]

Definitions
Similar constructs are defined differently across several research groups such as COMET, OMERACT, and HOME. As there is currently no consensus on the definitions, we would like to explicitly state the definitions that are being used in the COMET Delphi study in order to avoid any possible misinterpretations.

Core outcome set (COS)
A COS is an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. A COS includes all relevant outcomes of a specific health condition within a specified setting (the OMERACT definition refers to 'core domain set' whereas the HOME definition refers to 'core outcome domains').

Generic core outcome set (GOS)
A GOS is an agreed minimum set of *generic* outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. In this study, the GOS is intended to be applied for the assessment of various, unrelated skin diseases that are treated with different types of lasers.

Outcome and outcome domain
Throughout this report, the definition of "outcome" refers to a single construct that can be measured as a standalone item (e.g. 'erythema'), while the term "outcome domain" or "domain" is an umbrella term for a group of associated outcomes (e.g. 'signs as assessed by physician').

Outcome measurement instrument
An outcome measurement instrument refers to how the outcome is being measured (the tool used to assess the outcome). An outcome measurement instrument can be a single question, a questionnaire, a performance-based test, a physical examination, a laboratory measurement, an imaging technique, and so forth (the HOME definition refers to 'outcome measure').

SUPPLEMENTARY FILE 2

A list of invited patient support groups for the Delphi survey

Name of Society
Hidradenitis Patiëntenvereniging (NL)
Nevus Netwerk Nederland (NL)
Nevus Outreach (US)
Nevus Support (AU)
Neurofibromatose Vereniging Nederland (NL)
Vereniging Wijnvlek Sturgeweber syndroom (NL)
Sturge-Weber-Foundation (US)
Vitiligo patientenvereniging (NL)
National Vitiligo Foundation (US)

CHAPTER 3

A Systematic Review of Outcome Reporting in Laser Treatments for Dermatological Diseases

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Abstract

The standardization of outcome reporting is crucial for interpretation and comparison of studies related to laser treatment of skin disorders. In collaboration with the Cochrane Skin-Core Outcome Set Initiative (CS-COUSIN), a procedure has been proposed to find consensus on the most important generic outcome domains (*what* to measure) for implementation in the international Laser TrEAtment in Dermatology (LEAD) registry. As the first step in the development of a generic outcome set for the LEAD registry, we undertook a systematic review to identify outcomes, outcome measurement instruments, methods and definitions reported in recently published literature of laser treatments for skin disorders. A systematic search was conducted and generated a total of 707 papers. We assessed 150 studies including all types of studies involving laser treatments for the skin. Two researchers independently extracted the type, definition, and frequency of all outcomes and used outcome measurement instruments.

We identified 105 verbatim outcomes that were categorized into eight domains recommended by the COMET framework: appearance, long-term effects, physician and patient reported physical signs, satisfaction, health related quality of life, psychological functioning and adverse events. Heterogeneity in outcome reporting (e.g. categories and outcome measurement instruments) was high and definitions were insufficiently reported. There was a clear under representation of life impact domains, including satisfaction (23%) quality of life (3%) and psychological functioning (1%). Outcome reporting concerning laser treatments for the skin is heterogeneous. Standardized outcomes are needed for improving evidence synthesis. Results of this review will be used in the next step to reach consensus between stakeholders on the outcome domains to be implemented in the LEAD registry.

Introduction

During the past few decades, a growing number of skin laser treatments have rapidly evolved and increased their role in the field of dermatology. Today, laser surgery is considered the treatment of choice for a variety of skin disorders as well as aesthetic problems.[1,2] A variety of lasers facilitates treatment approaches not only for common skin diseases but also for uncommon but medically relevant skin disorders, including vascular, pigmented, inflammatory, adnexal and (pre) malignant skin conditions.[2–4] For most of these rare skin disorders, evidence derives from case reports and case series.[5] The combination of selective reporting of positive results and inadequate reporting of negative results might lead to overestimated treatment effects from a laser therapy exceeding those that are truly effective. However, evidence-based data is required when adopting laser treatment for routine use in such skin conditions. To overcome these issues and improve the quality and coherence of research, the European Laser Treatment (LEAD) Registry is established to initiate collaborative data pooling of a wide range of skin disorders.

An important aspect of guiding clinical practice is reporting patient-centered outcomes. The need for consistent use of outcomes has already been highlighted in various specialties including surgery, emergency medicine, anesthesia, dermatology, oncology, and internal medicine.[6–11] Understanding which outcomes are relevant to patients, health care professionals and researchers with an overview of current outcomes, should be a research priority, however, studies in the field of laser dermatology are lacking.[6] Based on the guidelines established by The Core Outcome Measures in Effectiveness Trials (COMET) Initiative (www.comet-initiative.org) and the Cochrane Skin– Core Outcome Set Initiative, a procedure has been proposed deciding upon the most relevant outcome domains (*what* to measure) for the LEAD Registry, determined by consensus.[7,12,13] For implementation in the registry, the set of generic outcome domains needs to be broadly applicable across a spectrum of skin diseases for different laser treatments. In addition, generic outcomes are proposed as standardized, suitable, responsive, and clinically relevant to improve the possibility of identifying effective laser treatments for various skin disorders and without being too burdensome to collect.[7,12,14]

As the first step in developing a set of generic outcome domains for the LEAD registry, the aim of the present study is to summarize current outcomes, outcome measurement instruments, methods and definitions in the recent literature on laser treatments for skin disorders. The secondary objective is to assign the list of outcomes to standardized domains using the standardized COMET taxonomy. Results of this review will be used in the next step to reach consensus between stakeholders on the outcome domains to be implemented in the LEAD registry.

Materials and Methods

This systematic review has been conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. [15] This systematic review adheres to a predefined protocol in accordance with the COMET Handbook which provides guidelines for development of a Core Outcome Set (COS).[12,16] The protocol is registered at the Cochrane Skin - Core Outcomes Set Initiative and at the COMET Initiative database.[6]

Data Sources and searches

Searches were performed in MEDLINE and Embase, according to guidelines on COS development.[7] Randomized Controlled Trials, cohort studies, case series and case reports that assess any type of laser treatment for skin disorders with any etiology were eligible for inclusion. There was no restriction on age, sex and localization. We excluded studies other than human subjects, laser assisted drug delivery, low laser level therapy and laser treatments for the purpose of skin rejuvenation**.** The length of the systematic review period was limited to 5 years to identify current outcomes**.** Further details of the search strategy using validated terms can be found in supplemental data 1.

Study Selection

Titles and abstracts were screened independently by two reviewers (F.F. and D.T.). Table 1 provides an overview of the eligibility criteria. Full-text articles were retrieved if the abstract passed the first eligibility screening or provided insufficient information. Discrepancies were resolved by discussion with a third senior review author (A.W.).

Table 1. Inclusion and exclusion criteria for the systematic literature review selection of outcomes in skin laser treatments.

	Inclusion criteria	Exclusion criteria
Patient population	Patients from any age and geographical location with any all medical skin disorders, regardless of their etiology and definition as common or exceptional such as orphan skin diseases	Non-humans
Study design	RCTs, cohort studies, case series, case reports	Systematic reviews, abstracts and expert opinions
Intervention	Skin laser treatment of the skin with exclusive therapeutic purpose	Laser assisted drug delivery, low laser level therapy, laser therapy for cosmetic indications (i.e. therapy with no therapeutic purpose)
Outcomes	Physician reported outcomes, patient reported outcomes, outcome measurement instruments	
Publication	All studies conducted between 2013-2017	

Data extraction and outcome reporting information

From each included study, the following data was collected: i) author; ii) year of publication; iii) country; iV) study design; V) cutaneous indication; Vi) type of laser treatment. All clinical outcomes and, their definitions and outcome measurement instruments were extracted and listed in tables. Clinical outcomes are defined as end-points measured by clinicians or researchers with the exclusion of outcomes that are physiological or biochemical in nature. Outcomes were considered as defined when explanations or citations were provided

Verbatim outcomes were initially reviewed by two reviewers (F.F. and D.T) and, for the purpose of presenting the results, classified according to the standardized taxonomy for outcomes proposed by the COMET initiative.[17] The taxonomy contains 38 domains within 5 core areas: mortality/survival; physiological/clinical; life impact; resource use; adverse events. Discrepancies in classifying verbatim outcomes were resolved by discussion with a third senior review author (A.W.). Previous outcome reviews have shown that 100 studies were sufficient to capture the most important outcomes.[8] Initially, we analyzed 80 articles for constructing the list of domains. We continued including studies for analysis until saturation was reached. The outcomes and outcome measurement instruments identified were summarized qualitatively and percentages were calculated.

Results

Studies identified

The systematic search generated a total of 712 papers. After removing duplicates, 707 papers remained of which the title and abstract were screened (flowchart, Fig. 1). Of these, we identified 350 potentially eligible papers that were sought for full-text screening. Finally, 326 papers were eligible for verbatim extraction and mapping to the standardized COMET taxonomy.[17] The first 80 articles formed an initial long list of outcomes assigned to standardized domains. The next 70 articles did not yield any new outcome domains. Therefore, we stopped screening new articles. There were 28 RCTs, 42 prospective studies, 27 retrospective studies, 53 case reports or series (Fig.1). Supplemental table 1 provides the main characteristics of all included studies.

Outcomes reported

In total, there were 105 different individual clinical outcomes extracted verbatim from the 150 included studies. All outcomes were categorized into one of the eight outcome domains: appearance, long-term effects, physician and patient reported physical signs, satisfaction, health related quality of life, psychological functioning and adverse events. The eight domains are reported and defined in Table 2. Extracted domains, outcomes and their associated outcome measurement instruments used in studies can be found in supplemental table 2 and 3, respectively.

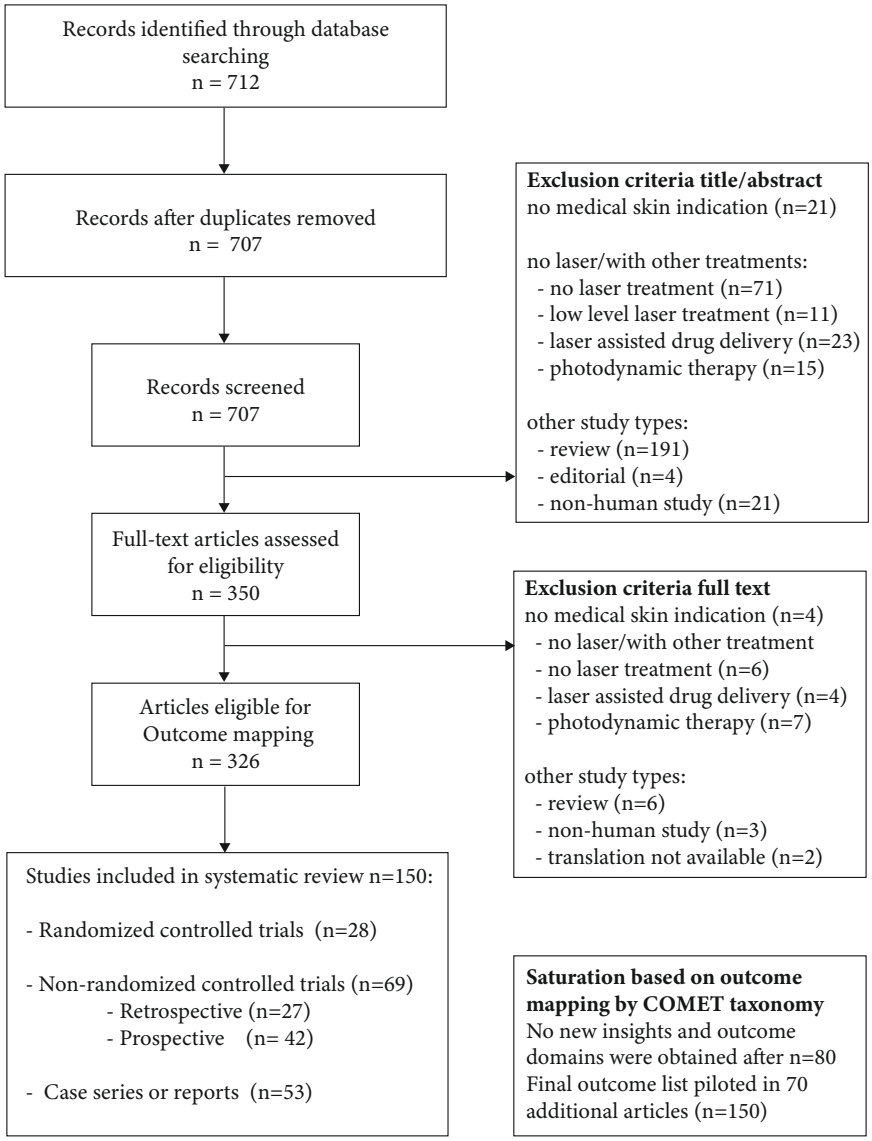

Figure 1. Flowchart of screening and selection procedure.

Table 2. Core areas, outcome domains, definitions and individual outcomes categorized in each outcome domain.

Core area [17]	Domain	Definition of domains	Number of individual outcomes in each domain	Frequency of studies reporting the domain
Physical/ clinical	Appearance by observer assessment	The way the lesion looks on the outside, judged by others, e.g. clearance or improvement of lesion. [21]	6	116 (77%)
	Long-term effects	Effects of the laser treatment lasting, staying or extending over a long period of time starting from 1 year or more.	2	34 (23%)
	Physical signs by observer assessment	Skin lesion morphology and consequences of laser treatment reported by health care providers, e.g. intensity of pigmentation or erythema	25	56 (25%)
	Physical signs by patient assessment	Signs perceptible by the patient, e.g. pruritus, burning.	11	20 (13%)
	Pain	Sensation of unpleasant feeling indicating potential or actual damage to some body structure felt all over, or throughout the body. [21]	1	25 (17%)
Life impact	Satisfaction	Satisfaction Fulfilment of one's wishes, expectations, or needs, or the pleasure derived from this. Divided into - Satisfaction with treatment services: patient's satisfaction with care received, including treatment and care providers. - Satisfaction with cosmetic result: patient's satisfaction with the cosmetic result of surgery - Satisfaction with laser treatment (overall): patient's rating of global satisfaction with treatment needs, or the pleasure derived from this.[11,21]	3	35 (23%)

Table 2. Continued.

Core area [17]	Domain	Definition of domains	Number of individual outcomes in each domain	Frequency of studies reporting the domain
	Health related quality of life (HRQoL)	Well-being reflecting subjective or objective judgement concerning health related aspects of an individual's existence.[11,21]	1	4 (3%)
	Psychological Functioning - Mood - Self-esteem - Self-image	Cognitive, emotional and behavioural responses at a personal level. Psychological Patient's levels of anxiety, depression and anger. Anxiety refers to fear, extreme worrying and hyper- arousal symptoms. Depression refers to negative mood, loss of self-confidence Self-esteem, loss of motivation and enjoyment. [11,21]	2	2 (1%)
Adverse events	Adverse events	Any untoward medical occurrence in a patient or clinical investigation subject treated with any other form of therapy which does not necessarily have to have a causal relationship with this treatment. [11,21]	37	78 (52%)

Appearance by observer assessment

There were eight individual outcomes categorized in the appearance domain recorded in 77% of all studies. The most frequently reported appearance-related individual outcomes were 'clinical improvement' and 'clearance' in 55% and 17% of studies, respectively. The five remaining individual outcomes were each reported in fewer than 7 studies (Supplemental table 2)

Measurement of outcome domains appearance Individual outcomes related to appearance were measured using a great variety of outcome measurement instruments (verbatim categories, grading and classification of percentiles). Measurement 'categories' refer to verbatim scales (e.g. 'improvement' to 'no improvement'). Other scales included percentiles by grading with quartiles, quintiles etc. (e.g. grade 1:<2%, grade 4: 75%–100%) and verbatim classification by percentiles (e.g. 0-25% :' worse', >75%: 'excellent'). All outcome measurement instruments used in 100 studies are summarized in supplemental table 3.

In total, there were 27 outcome measurement instruments with 30 variable verbatim categories, and 20 different scales used within the appearance domain. The most frequently used outcome measurement instruments for assessing outcomes was assessment by two or three independent dermatologists of before and after photographs (28%) and clinical live assessment (19%). Regarding outcome measurement instruments, there were 57% of studies using categorical verbatim scales. Of these 57% of studies, the three most frequently used categorical verbatim scales were '(no) improvement' (14%), '(no) recurrence' (13%) and '(no) clearance' (10%). Thirty-seven (25%) studies used grading percentiles and 17% of studies used measurement by categorization of percentiles with 20 different ways of reporting and unique definitions. For example, Huang et al.[18] and Yuan et al.[19] (see supplemental table 1) both used the '<25%, 25–49%, 50–74%, >75%' quartiles, but one study reported 'marked improvement' as 50-74% while another reported 'marked improvement' as >75%. All types and unique definitions of outcome measurement instruments are summarized in supplemental table 3.

Physical signs by observer assessment

There were 28 individual outcomes categorized in the physical signs by observer assessment domain recorded in 37% of all studies (Supplemental table 3). The signs of skin lesions were identified and related to morphology such as pigmentation aspects, vascular aspects and hair or nail aspects. Of the 37% of studies, the most frequently reported individual outcomes was erythema (13%). The majority of studies combined assessment of individual features or characteristics with global photographic assessment and disease specific assessment. Physicians global assessment scale (PGA) was used in 3% studies for evaluating physical signs. (Supplemental table 3)

Physical signs by patient assessment

There were eleven individual outcomes categorized in the physical signs by patient assessment domain recorded in 13% of all studies (Supplemental table 2). Generic terms that were used related to overall state and severity of disease, and overall aspects of the skin, such as the outcome of improvement in 3% of studies. In total, 4% of studies used patient reported questionnaires and 4% of studies used patient assessments for evaluating physical signs. (Supplemental table 3)

Long-term effects

There were two individual outcomes categorized in the long-term effects domain recorded in 23% of all studies with 'recurrence' being most frequently reported (20%). There were no studies adopting a predefined definition of the time to recurrence.

Health related quality of life (HRQoL)

In 3% of studies assessing the outcome of HRQoL was used (Table Supplemental table 2). Outcome measurement Instruments used were Dermatology Life Quality Index (DLQI) Skindex-16, Burn Specific Health Scale (BSHS-B) and a specific 8-question survey with limited information on the assessed items (Supplemental table 3).

Psychological Functioning

There was one study that reported outcomes related to the psychological functioning domain. This domain included the outcomes of anxiety, depression and body image dissatisfaction. Two questionnaires, the Hospital Anxiety and Depression Scale (HADS) and the Appearance Scale (ASWAP), were used. (Supplemental table 3).

Satisfaction

There were three individual outcomes categorized in the satisfaction domain recorded in 23% of all studies. The most frequent reported individual outcome was 'overall satisfaction' (21%).

Similar to the outcomes within the domain of appearance, a variety of outcome measurement instruments were used to assess the outcome of satisfaction. There were 11% of studies reporting seven different verbatim categorical measurement outcomes (e.g. 'very satisfied' to 'not satisfied') to measure satisfaction. Scales such as percentiles by grading with quartiles, quintiles etc. (e.g. grade 1: 0–24, grade 4: 75–100), percentiles by classification (e.g. 0-25 :' not satisfied', >75: 'very satisfied') were used by 7% of studies. The visual analogue scale (1-10 or 1-100) was used in 4% of all studies to measure satisfaction (Supplemental table 3). Finally, another 1% of all trials used a general questionnaire, such as PSQ-18, or single specific questions (e.g. Has your confidence improved as a result of the laser treatment?) (Supplemental table 3).

Adverse events

There were 46 individual outcomes categorized in the adverse events domain recorded in 52% of all studies. The most frequently reported individual outcomes were 'erythema' (25%), 'hypopigmentation' (19%), 'hyperpigmentation' (13%) and 'scarring' (16%) (Supplemental table 3). The outcome of pain (limited to pain, tolerability) was assessed in 17% studies, using a visual analogue scale or undefined scale. Pain was generally briefly in the results or discussion section of studies. In most articles, no information was provided on measurement, frequency, severity and time frames of post-treatment complications.

Discussion

Summarizing outcomes in current literature should be a research priority, however, studies that report outcomes are scarce in the field of laser surgery. This systematic review has identified a wide diversity in the selection, definition and reporting of clinical outcomes of laser surgery for the skin. In total, 105 outcomes were identified in 150 articles and were categorized into 8 outcome domains. Similar individual outcomes were often defined differently within outcome domains, e.g., 'clearance', 'improvement' were both presented within the appearance domain. Certain domains were seen to be underrepresented. Outcomes concerning long-term effects of laser treatments were infrequently reported and inconsistently defined. A similar clear under representation was apparent in life impact domains, including satisfaction (23%) quality of life (3%) and psychological functioning (1%). The underrepresentation is remarkable since the inclusion of patients 'perspectives about their health in the evaluation of treatments is a key element of the patient-centered model of healthcare.[13,16,17] This review also highlights that different outcome measurement instruments were used for the same individual outcomes. For example, we identified 53 different outcome measurement instruments within the appearance domain, many not comparable. Similar variations were identified for the assessment of the satisfaction domain, with the use of 17 different outcome measurement instruments. Various outcome measurement instruments with unknown measurement properties are used in current studies on laser treatments, which make analysis and comparison of their results uncertain.

To date, no systematic review provided a detailed, comprehensive summary and analysis of outcome reporting in skin laser surgery. However, quality of reporting outcomes has previously been described in surgery and dermatology.[8–10] Similar to our results, authors reported underrepresentation of patient-reported and long-term outcomes besides the need for more agreement about what should be measured in the evaluation of skin disorders. The implications of waste and bias in research due to different outcomes, also described by Chalmers and Glasziou[20], highlights the urgent need to define outcome sets for specific clinical areas. [10,20] Research identifying patients' urgencies with skin disorders is limited to a few common skin disorders, and further evidence is needed to ensure patients 'main concerns are accurately represented. Regarding measurement of outcomes, we did not assess the measurement properties of the outcome measurement instruments for laser treatments. Evaluation of the measurement properties, such as validity, reliability and responsiveness of outcome measurement instruments is beyond the scope of this review. No recommendations are therefore to be made about outcome instruments.

This review has several limitations. The first limitation concerns the methodological approach of summarizing outcomes of many different indications across various

available laser treatments. However, given the long duration and huge effort of the COS development and validation process, it is difficult to reach consensus on outcomes for each skin condition apart. All the more as there are hundreds of uncommon dermatological conditions for which laser treatments have been documented and published. Therefore, we decided to develop a generic set of outcomes to be used in the LEAD registry. The current data suggest that the outcome domains are most likely very similar for the different skin conditions.

Secondly, the search of this review was restricted to articles published between January 2013 and December 2017. Older studies may have identified more outcomes, although we have reached the point of saturation in our review. Besides, we were mainly interested in currently used outcomes in laser treatments for dermatological disorders.

Regarding the LEAD registry, relevant new laser treatments and outcomes specific to treatments or diseases need continuously to be considered. In the future, we plan to mitigate absent information by engaging patient and health-care professionals to propose additional outcomes in the international Delphi consensus.

In summary, this review has shown substantial heterogeneity in outcome reporting in laser treatments for dermatological disorders with a high variety of individual outcomes, outcome measurement instruments across the recent literature. An underrepresentation of patient-centered outcomes has also been highlighted.

Outcomes need to be relevant to both patients and healthcare professionals and generalizable to a range of laser treatments and dermatological indications. This study, in which we identified a list of potentially relevant outcome domains, is the first step towards the development of a generic outcome set in laser dermatology. Future work will survey the perspective of key stakeholders (patients, health professionals) by using the Delphi method for reaching consensus on the most important generic outcome domains to adopt in the LEAD registry.

Contributors

FF, AW, CP provided substantial contributions to the conception and design, acquisition of data, analysis and interpretation. FF and DT extracted the data. FF drafted the article. All authors edited and critically revised the paper and approved the final version.

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References

1. Gianfaldoni S, Tchernev G, Wollina U, Fioranelli M, Roccia MG, Gianfaldoni R, et al. An Overview of Laser in Dermatology: The Past, the Present and … the Future (?). *Open Access Maced J Med Sci*. 2017; **5**(4): 526–530.
2. Houk LD, Humphreys T. Masers to magic bullets: an updated history of lasers in dermatology. *Clin Dermatol. 2007*;**25(**5):434–42.
3. Chiang YZ, Al-Niaimi F, Ferguson J, August PJ, Madan V. Carbon dioxide laser treatment of cutaneous neurofibromas. *Dermatol Ther (Heidelb)*. 2012;**2**(1):1–6.
4. Ortiz AE, Zachary CB. Laser therapy for Hailey-Hailey disease: Review of the literature and a case report. *Dermatology Reports*. 2011 ;**3**(2):e28.
5. Gagne JJ, Thompson L, O'Keefe K, Kesselheim AS. Innovative research methods for studying treatments for rare diseases: methodological review. *BMJ*. 2014;**349**:g6802–g6802.
6. Comet initiative. Available at: http://www.comet-initiative.org/.
7. Prinsen CAC, Vohra S, Rose MR, King-Jones S, Ishaque S, Bhaloo Z, et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: Protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a "core outcome set." *Trials*. 2014;**15**(1).
8. Whistance RN, Forsythe RO, McNair AGK, Brookes ST, Avery KNL, Pullyblank AM, et al. A systematic review of outcome reporting in colorectal cancer surgery. *Color Dis*. 2013;**15**(10):e548-60.
9. Busard CI, Nolte JYC, Pasch MC, Spuls PI. Reporting of outcomes in randomized controlled trials on nail psoriasis: A systematic review. *Br J Dermatol*. 2017; 1**78** (3): 640–649.
10. Eleftheriadou V, Thomas K, van Geel N, Hamzavi I, Lim H, Suzuki T, et al. Developing core outcome set for vitiligo clinical trials: International e-Delphi consensus. *Pigment Cell Melanoma Res*. 2015;**28**(3):363–9.
11. de Kleuver M, Faraj SSA, Holewijn RM, Germscheid NM, Adobor RD, Andersen M, et al. Defining a core outcome set for adolescent and young adult patients with a spinal deformity. *Acta Orthop*. 2017;**88**(6):612–8.
12. Schmitt J, Deckert S, Alam M, Apfelbacher C, Barbaric J, Bauer A, et al. Report from the kick-off meeting of the Cochrane Skin Group Core Outcome Set Initiative (CSG-COUSIN). *Br J Dermatol*. 2016 **;174**(2):287-95.
13. Williamson PR, Altman DG, Bagley H et al. The COMET handbook. *Trials* 2017; **18**(Suppl. 3):280.
14. Kirkham JJ, Gorst S, Altman DG, Blazeby JM, Clarke M, Devane D, et al. Core Outcome Set–STAndards for Reporting: The COS-STAR Statement. *PLoS Med*. 2016;**13**(10).
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Med* **6**(7): e1000100. available at: https://doi.org/10.1371/journal.pmed.1000100.
16. Kirkham JJ, Gorst S, Altman DG, Blazeby J, Clarke M, Devane D, et al. COS-STAR: A reporting guideline for studies developing core outcome sets (protocol). *Trials*. 2015;**16**(1).
17. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. *J Clin Epidemiol*. 2018;**96**:84–92.

18. Huang Y, Zhuo F, Li L. Enhancing hair growth in male androgenetic alopecia by a combination of fractional CO2laser therapy and hair growth factors. *Lasers Med Sci.* 2017;**32(**8):1711–8.

19. Yuan J, Chen H, Yan R, Cui S, Li YH, Wu Y, et al. Fractional CO2lasers contribute to the treatment of stable non-segmental vitiligo. *Eur J Dermatology.*2016;**26**(6):592–8.

20. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet (*London, England). 2009;**374**:86-8.

21. WHO. WHO | International Classification of Functioning, Disability and Health (ICF). *WHO.* 2017. Available at: http://apps.who.int/classifications/icfbrowser/.

SUPPLEMENTARY DATA 1

Systematic review search strategies

Pubmed
1.“Skin” [Majr MeSH]
2.“cutaneous” [Majr MeSH]
3.“dermatology” [Majr MeSH]
4. “Skin Diseases”
5. 1 or 2 or 3 or 4
6.“laser” [Majr MeSH]
7.“alexandrite laser” [MeSH Terms]
8 “laser, pulsed dye” [MeSH Terms]
9. “er yag” [MeSH Terms]
10. “laser, nd yag” [MeSH Terms]
11. “laser, ruby” [MeSH Terms]
12. “laser, ysgg” [MeSH Terms]
13. “laser, argon” [MeSH Terms]
14. “laser, ktp” [MeSH Terms]
15. “laser, q switched” [MeSH Terms]
16. “laser, carbon dioxide” [MeSH Terms]
17. “laser, co2” [MeSH Terms]
18. “laser, diode” [MeSH Terms]
19. “thullium laser”
20. “fluoride laser”
21. “fractional laser”
22. “fractional CO2 laser”
23. “non-ablative fractional laser”

24.“Humans[Mesh]
25. “last 5 years”[PDat]
26. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
26. 5 and 26

Embase:
1. #1, Skin.mp. or exp skin/
2. #2, cutaneous.mp.
3. #3, dermatology.mp. or exp dermatology/

4. #4, skin diseases.mp. or exp skin disease/
5. #5, laser.mp. or exp laser/
6. #6, laser treatment.mp.
7. #7, laser therapy.mp.
8. #8, skin laser therapy.mp.
9. #9, exp argon laser/ or exp frequency doubled neodymium YAG laser/ or exp thulium YAG laser/ or exp dye laser/ or exp gallium aluminum arsenide laser/ or exp neodymium laser/ or exp pulsed dye laser/ or exp carbon dioxide laser/ or exp excimer laser/ or exp YAG laser/ or exp alexandrite laser/ or exp argon fluoride laser/ or exp gas laser/ or exp laser surgery/ or exp erbium YAG laser/
10. #10, nd YAG laser.mp.
11. #11, non-ablative fractional laser.mp.
12. #12, CO2 laser.mp.
13. #13, fractional CO2 laser.mp.
14. #14, carbon dioxide laser.mp. or exp carbon dioxide laser/
15. #15, q switched laser.mp.
16. #16, nd YAG laser.mp.
17. #17, exp symptom assessment/ or exp symptom/ or symptoms.mp.
18. #18, outcome assessment.mp. or exp outcome assessment/
19. #19, treatment outcome.mp. or exp treatment outcome/
20. #20, exp treatment outcome/ or exp outcome assessment/ or outcome.mp.
21. #1 or #2 or #3 or #4
22. #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
23. #17 or # 18 or #19 or #20
24. #21 and #22
25. #23 and #24
26. 25 and 2013:2017.(sa_year).
27. 26 and “human” [Subjects]

Supplemental table 1. Characteristics of all included laser studies[1] in this review

First Author and Reference	Year	Design	Sample size (n)	Indication	Laser intervention
1. Ochi (1)	2017	Retrospective	107	Acne scars	Fractional CO2
2. Heng (2)	2017	Retrospective	64	Xanthelasma palpebrarum	Q-switched Nd:YAG
3. Huang (3)	2017	RCT	28	Alopecia androgenetica	Fractional CO2
4. Friedmann (4)	2017	Case report	1	Cutaneous Argyria from a Nasal Piercing	Q-Switched Alexandrite
5. Lee (5)	2017	Prospective	1	Epidermal nevus syndrome	Er:YAG
6. Kaminaka (6)	2017	RCT	10	Melasma and lentigines	Q-switched Nd:YAG
7. Choi (7)	2017	RCT	45	Nodular basal cell carcinoma	Fractional CO2
8. Geddes (8)	2017	Retrospective	11	Melasma	PDL + Thullium fractional
9. Zaouak (9)	2017	Case report	1	Cutaneous sarcoïdosis	PDL
10. Murthy (10)	2017	Retrospective	29	Symptomatic or disfiguring vascular malformations	PDL
11. Özdemir (11)	2017	Case series	7	Kaposi sarcoma	Nd:YAG
12. Zane (12)	2017	RCT	240	Basal cell carcinoma	CO2
13. Doh (13)	2017	Prospective	6	Capillary malformations	Nd:YAG
14. Çalişkan (14)	2017	Case report	1	Pyoderma gangrenosum	Er:YAG
15. Chu (15)	2017	Case series	3	Lichen amyloidosis	Fractional CO2
16. Zhu (16)	2016	Case report	1	Nevus comedonicus	CO2
17. Poetschke (17)	2017	Case-control	10	Hypertrophic burn scars	CO2
18. Foering (18)	2017	Case report	1	Pseudoxanthoma	Fractional, non-ablative
19. Vanaman Wilson (19)	2017	Case report	1	Under-Eyelid Pigmentation	Pico Alexandrite
20. Lee (20)	2017	Case report	1	Palmoplantar hypokeratosis	755-nm Alexandrite
21. Alavi (21)	2017	RCT	41	Melasma	Q-Switched Nd:YAG + Fractional Er:YAG

1 For full references, see the extended list below the table.

Supplemental table 1. Characteristics of all included laser studies in this review

First Author and Reference	Year	Design	Sample size (n)	Indication	Laser intervention
22. Piccolo (22)	2017	Prospective	20	Onychomycosis	Nd:YAG
23. Kelati (23)	2017	Case report	1	Elastosis Perforans Serpiginosum	Fractional CO2
24. Issler-Fisher (24)	2017	Prospective	1	Burn scars	Fractional CO2
25. Vanarase (25)	2017	RCT	60	Black tattoos	Q-switched Nd:YAG versus CO2
26. Bae (26)	2017	Prospective	10	Port wine stains	PDL
27. Radmanesh (27)	2017	Prospective	17	Cutaneous Leishmaniasis	PDL
28. Osman (28)	2017	RCT	30	Acne scars	Er: YAG
29. Lee (29)	2017	Case report	2	Melanonchia	Q-Switched Alexandrite
30. Kim (30)	2017	Prospective	19	Periorbital Syringomas	Nd:YAG
31. Strand (31)	2017	Prospective	50	Rosacea	PDL
32. Soriano (32)	2016	Case series	8	Larva migrans	CO2
33. Kim (33)	2016	RCT		Rosacea	PDL
34. Yuan (34)	2016	Prospective	20	Stable non-segmental vitiligo	Fractional CO2
35. Osman (35)	2017	RCT	20	Verrucous epidermal nevus	CO2 versus Er:YAG
36. Shin (36)	2017	RCT	72	Viral warts	Er:YAG
37. Kang (37)	2017	Retrospective	516	Solar lentigines	Q-Switched Nd: YAG
38. Alshami (38)	2016	Prospective	240	Palmoplantar warts	Nd:YAG
39. Karsai (39)	2017	RCT	20	Onychomycosis	Nd:YAG
40. Shalaby (40)	2016	RCT	17	Scleroderma	Fractional CO2
41. Lee (41)	2016	Retrospective	48	Melasma	Alexandrite
42. Yue (42)	2016	Prospective	30	Melasma	Q-switched Nd:YAG
43. Zeng (43)	2016	Prospective	8	Nodular congenital melanocytic naevus	CO2 + Q-switched Nd:YAG
44. Tian (44)	2016	Cases report	2	Melasma	Fractional Er:YAG + Q-switched Nd:YAG
45. Vachiramon (45)	2016	RCT	24	Keratosis Pilaris	Fractional CO2
46. Han (46)	2016	Case report	1	Fox Fordyce disease	Fractional Erb glass
47. Balarama (47)	2016	Retrospective	3	Becker's nevi	Fractional non ablative
48. Fremli (48)	2016	Case report	1	Hyperpigmentation within a plexiform neurofibroma	Q-switched Nd:YAG
49. Shrof (49)	2016	Retrospective	30	Chronic hand and foot eczema	308 nm Excimer
50. Tartar (50)	2016	Case report	1	Cutaneous Lymphoma	Fractional CO2

Supplemental table 1. Characteristics of all included laser studies in this review

First Author and Reference	Year	Design	Sample size (n)	Indication	Laser intervention
51. Ali (51)	2016	Retrospective	45	Dermatosis papulosis nigra	CO2
52. Liu (52)	2016	Prospective	37	Acne vulgaris	Er:YAG
53. Baumgartner (53)	2016	Case report	1	Angiokeratoma	PDL + Alexandrite
54. Moore (54)	2016	Case report	1	Minocycline-Induced Pigmentation	Pico Alexandrite
55. Penev (55)	2016	Case report	1	Disseminated trichoblastomas	CO2
56. Kauvar (56)	2017	Prospective	34	Tattoos	1064/532-nm Pico
57. Noh (57)	2016	RCT	8	Facial lentigines	Q-Switched Nd:YAG
58. Zeng (58)	2016	Case series	11	Angiokeratoma of Fordyce	Nd:YAG
59. Basnett (59)	2015	Case series	1	Leishmaniasis	Fractional CO2
60. Rodrigues (60)	2015	Case series	3	Minocycline-Induced Pigmentation	Pico Alexandrite
61. Ibrahim (61)	2016	RCT	22	Fordyce angiokeratoma	Pulsed dye vs Nd:YAG
62. Henes (62)	2015	Prospective	18	Cervical neoplasias and condyloma	Thullium
63. Chen (63)	2015	Retrospective	66	Osmidrosis	Nd:YAG
64. Rivers (64)	2015	case report	1	Glomuvenous malformation	Nd:YAG
65. Kim (65)	2015	RCT	5	Café-au-lait macules	Q-switch Nd:YAG
66. Ge (66)	2015	Retrospective	11	Labial lentigines with Peutz-Jeghers Syndrome	Q-switch Nd:YAG
67. Rodriguez Ruiz (67)	2016	Retrospective	7	Ulcerated infantile hemangioma	PDL+ propanol
68. Lloyd (68)	2015	Case report	1	Cutaneous siderosis	Alexandrite
69. Wen (69)	2015	RCT	17	Naevus of Ota	Nd:YAG
70. Zhong (70)	2015	Prospective	794	Infantile hemangioma	Nd:YAG
71. Esmat (71)	2015	RCT	25	Amyloidosis	Fractional CO2
72. Phillips (72)	2015	Cases report	3	Ulcers	Fractional CO2
73. Alabdulrazzaq (73)	2015	Case report	6	Yellow tattoo clearance	Pico
74. Gurel (74)	2015	RCT	42	Seborrheic keratosis	Er:YAG

Supplemental table 1. Characteristics of all included laser studies in this review

First Author and Reference	Year	Design	Sample size (n)	Indication	Laser intervention
75. Vachiramon (75)	2015	RCT	15	Melasma	Q-switched Nd:YAG + peeling
76. Lee (76)	2015	RCT	24	Melanocytic nevi	Er:YAG + Alexandrite
77. El tatawy (77)	2015	RCT	40	Onychomycosis	Nd:YAG
78. Ortiz (78)	2015	Prospective	10	Basal cell carcinoma	Nd:YAG
79. Campuzano Garcia (79)	2015	Case report	1	Hailey-Hailey disease	Fractional CO2
80. Zeng (80)	2015	Case report	1	Colloid millium	Fractional non-ablative
81. Goldberg (81)	2015	Prospective	25	Verruca vulgaris	Nd:YAG
82. Korkmaz (82)	2015	Retrospective	73	Benign eyelid lesions	Argon
83. Krakowski (83)	2015	Case report	1	Pearly penile papules	CO2
84. Goo (84)	2015	Case series	2	Rosacea	Q-switched Nd:YAG
85. Su (85)	2015	Prospective	50	Mibelli angiokeratoma	PDL
86. Shi (86)	2014	Retrospective	848	Port wine stains	PDL
87. Brauer (87)	2015	Prospective	20	Facial acne scarring	Pico
88. Ibrahim (88)	2015	RCT	23	Keratosis Pilaris	810-nm Diode
89. Moneib (89)	2014	Prospective	24	Acne vulgaris	Fractional erbium glass
90. Yun (90)	2014	RCT	24	Melasma	Q-switched Nd:YAG
91. Smith (91)	2015	Retrospective	53	Recalcitrant warts	Nd:YAG
92. Hélou (92)	2014	Prospective	10	Vitiligo	Fractional CO2
93. Thomas (93)	2017	Prospective	147	Acne scarring, rosacea and photo aging	Fractional CO2, non-ablative, Nd:YAG, Er:YAG, PDL, Pico
94. Kaune (94)	2014	Retrospective	38	Infantile hemangioma	PDL+ Nd:YAG
95. Han (95)	2014	Case report	1	Lichen planus pigmentosus	Pigment
96. Deaver (96)	2014	Retrospective	6	Mycosis fungoides	Excimer
97. Eimpunth (97)	2014	Prospective	24	Melasma	CuBr
98. Dinsdale (98)	2015	RCT	19	Facial or upper limb telangiectasia as part of systemic sclerosis	PDL
99. Ma (99)	2014	Prospective	12	Angiofibromas	Fractional Nd:YAG
100. Kimura (100)	2014	Prospective	20	Refractory warts	Nd:YAG
101. Alghamdi (101)	2014	Prospective	11	Atrophic leishmaniasis	Fractional CO2
102. Lekakh (102)	2015	RCT	18	Acne vulgaris	PDL

Supplemental table 1. Characteristics of all included laser studies in this review

First Author and Reference	Year	Design	Sample size (n)	Indication	Laser intervention
103. Beleznay (103)	2014	Case Report	1	Lupus miliaris	Fractional CO2, non-ablative
104. Sajan (104)	2014	Retrospective	22	Hemangiomas of infancy (HOIs) and port-wine stains	PDL
105. Kutlubay (105)	2014	Case Report	1	Dystrophic calcinosis	CO2
106. Güngör (106)	2014	Prospective	20	Striae	Nd:YAG, Er:YAG
107. Lee (107)	2014	Case Report	1	Post-inflammatory hyperpigmentation	Thulium fiber fractional laser
108. Lee (108)	2015	Prospective	8	Melasma	Q-switched Nd:YAG
109. Bencini (109)	2015	Prospective	18	Poikiloderma of Civatte	Fractional Er:YAG, non-ablative
110. Zeng (110)	2014	Case report	5	Mibelli angiokeratoma	PDL, Nd:YAG
111. Kim (111)	2014	Prospective	13	Seborrheic keratoses	Alexandrite
112. Biondo (112)	2014	Case report	1	Nodular facial angiofibromas	CO2
113. Joo (113)	2014	Case report	1	Verruciform xanthoma	Fractional CO2
114. Hammami (114)	2015	Case report	1	Cutaneous siderosis	Q-switched Nd:YAG
115. Bjørn (115)	2014	RCT	13	Acne scars	Fractional CO2
116. Salas-Alanis (116)	2014	Case report	1	Hypertrichosis lanuginosa congenital	Diode
117. Shin (117)	2013	Prospective	40	Idiopathic guttate hypomelanosis	Fractional CO2
118. Pickert (118)	2014	Case report	1	Linear morphea	PDL
119. Zeng (119)	2014	Case report	2	Congenital melanocytic nevus	CO2
120. Zeng (120)	2014	Case report	1	Split ocular nevus	CO2
121. Alcántara-González (121)	2013	Retrospective	30	Venous malformations	PDL + Nd:YAG
122. Richard (122)	2014	Case series	5	Brooke-Spiegler cylindroma	CO2
123. Alcántara-González (123)	2013	Retrospective	22	Infantile hemangiomas	PDL + Nd:YAG
124. Norisugi (124)	2013	Case report	2	Lichen amyloidosis	CO2
125. Lapidoth(125)	2013	Prospective	17	Actinic Keratosis	Fractional Er:YAG
126. Tenna (126)	2013	Case report	1	Milia en plaque	Fractional CO2
127. Cameli (127)	2014	Prospective	10	Acne scars and Photoaging	Fractional CO2

Supplemental table 1. Characteristics of all included laser studies in this review

First Author and Reference	Year	Design	Sample size (n)	Indication	Laser intervention
128. Marmon (128)	2014	Prospective	10	Photodamage	1.440-nm diode fractional
129. Saelim (129)	2013	RCT	18	Keratosis Pilaris	Nd:YAG
130. Grillo (130)	2014	Prospective	32	Facial warts	PDL
131. Becher (131)	2014	Retrospective	647	Superficial vascular lesions	Nd:YAG
132. Su (132)	2014	Retrospective	48	Infantile Hemangiomas	PDL
133. Fioramonti (133)	2014	Retrospective	13	Angiofibromas in Tuberous Sclerosis	CO2+Erbium: YAG+PDL
134. Nguyen (134)	2014	Case report	1	Glomuvenous Malformations	PDL + Nd:YAG
135. Emer (135)	2013	Case series	2	Lupus Pernio	Q-switched Nd:YAG
136. Hilton (136)	2013	Retrospective	25	Melasma	Q-switched Ruby
137. Yelamos (137)	2014	Case report	1	Cutaneous lupus erythematosus	PDL
138. Kriechbaumer (138)	2013	Prospective	21	Neurofibromas	Er:YAG
139. Niwa Massaki (139)	2013	Retrospective	20	Melasma	Fractional thulium fiber
140. Bruscino (140)	2014	Case series	5	Dermatosis Papulosa Nigra	CO2
141. Alshami (141)	2014	Prospective	350	Melanocytic nevi	Nd:YAG
142. Serowka (142)	2014	Case series	5	Rhinophyma	CO2
143. Naouri (143)	2012	Case report	1	Candida tropicalis onychomycosis	Nd:YAG
144. Kavoussi (144)	2013	Prospective	74	Basal cell carcinoma	CO2
145. Van Drooge (145)	2013	Retrospective	32	Hypertrophic port-wine stains	Nd:YAG
146. Conti (146)	2013	Case report	1	Jessner-Kanof disease	PDL
147. Polder (147)	2013	Prospective	6	Seborrheic Keratoses	Fractional thulium
148. Choi (148)	2014	Prospective	19	Nevus of Ota	Q-switched Nd:YAG
149. Shumaker (149)	2013	Case report	1	Lymphangioma Circumscriptum	Fractional CO2
150. Halamchi (150)	2014	Prospective	8	Hereditary hemorrhagic telangiectasia	PDL

References

1. Ochi H, Tan L, Tan WP, Goh CL. Treatment of Facial Acne Scarring with Fractional Carbon Dioxide Laser in Asians, a Retrospective Analysis of Efficacy and Complications. *Dermatologic Surg.* 2017;43(9):1137–43.
2. Heng JK, Chua SH, Goh CL, Cheng S, Tan V, Tan WP. Treatment of xanthelasma palpebrarum with a 1064-nm, Q-switched Nd:YAG laser. *J Am Acad Dermatol.* 2017;77(4):728–34.
3. Huang Y, Zhuo F, Li L. Enhancing hair growth in male androgenetic alopecia by a combination of fractional CO2laser therapy and hair growth factors. *Lasers Med Sci.* 2017;32(8):1711–8.
4. Friedmann DP, Buckley S, Mishra V. Localized Cutaneous Argyria from a Nasal Piercing Successfully Treated with a Picosecond 755-nm Q-Switched Alexandrite Laser. *Dermatologic Surgery.* 2017;143: 1094–5.
5. Lee J-H, Lee H-E, Lee Y, Seo Y-J, Lee J-H, Im M. Er:YAG laser treatment of epidermal nevus syndrome. *Int J Dermatol.* 2017;56(1):e13–5.
6. Kaminaka C, Furukawa F, Yamamoto Y. The Clinical and Histological Effect of a Low-Fluence Q-Switched 1,064-nm Neodymium:Yttrium-Aluminum-Garnet Laser for the Treatment of Melasma and Solar Lentigenes in Asians: Prospective, Randomized, and Split-Face Comparative Study. *Dermatologic Surg.* 2017;43(9):1120–33.
7. Choi SH, Kim KH, Song KH. Er:YAG ablative fractional laser-primed photodynamic therapy with methyl aminolevulinate as an alternative treatment option for patients with thin nodular basal cell carcinoma: 12-month follow-up results of a randomized, prospective, comparative trial. *J Eur Acad Dermatology Venereol.* 2016;30(5):783–8.
8. Geddes ERC, Stout AB, Friedman PM. Retrospective analysis of the treatment of melasma lesions exhibiting increased vascularity with the 595-nm pulsed dye laser combined with the 1927-nm fractional low-powered diode laser. *Lasers Surg Med.* 2017;49(1):20-26.
9. Zaouak A, Koubaa W, Hammami H, Fenniche S. Unconventional use of fractional ablative CO2 laser in facial cutaneous sarcoïdosis. *Dermatol Ther.* 2017;30(6):e12569.
10. Murthy AS, Dawson A, Gupta D, Spring S, Cordoro KM. Utility and tolerability of the long-pulsed 1064-nm neodymium:yttrium-aluminum-garnet (LP Nd:YAG) laser for treatment of symptomatic or disfiguring vascular malformations in children and adolescents. *J Am Acad Dermatol.* 2017;77(3):473–9.
11. Özdemir M, Balevi A. Successful Treatment of Classic Kaposi Sarcoma With Long-Pulse Neodymium-Doped Yttrium Aluminum Garnet Laser. *Dermatologic Surg.* 2017; 43(3):366-370.
12. Zane C, Facchinetti E, Arisi M, Ortel B, Calzavara-Pinton P. Pulsed CO2 Laser Ablation of Superficial Basal Cell of Limbs and Trunk. *Dermatologic Surg.* 2017;43(7):920–7.
13. Doh EJ, Ohn J, Kim MJ, Kim YG, Cho S. Prospective pilot study on combined use of pulsed dye laser and 1% topical rapamycin for treatment of nonfacial cutaneous capillary malformation. J *Dermatolog Treat.* 2017;28(7):672–7.
14. çalisçan E. as pyoderma gangrenosum. *Dermatol Surg.* 2017;43(11):1405–7.
15. Chu H, Shin JU, Lee J, Park CO, Lee KH. Successful treatment of lichen amyloidosis accompanied by atopic dermatitis by fractional CO2laser. *J Cosmet Laser Ther.* 2017;19(6):345–6.
16. Zhu C, Sun A. Ultrapulse carbon dioxide laser treatment for bilateral facial nevus comedonicus: A case report. *Dermatol Ther.* 2017;30(3).

17. Poetschke J, Dornseifer U, Clementoni MT, Reinholz M, Schwaiger H, Steckmeier S, et al. Ultrapulsed fractional ablative carbon dioxide laser treatment of hypertrophic burn scars: evaluation of an in-patient controlled, standardized treatment approach. *Lasers Med Sci*. 2017;32(5):1031–40.

18. Foering K, Torbeck RL, Frank MP, Saedi N. Treatment of Pseudoxanthoma elasticum-like papillary dermal elastolysis with non-ablative fractional resurfacing laser resulting in clinical and histologic improvement in Elastin and Collagen. *J Cosmet Laser Ther.* 2018;20(7-8):382-384.

19. Vanaman Wilson MJ, Alkhonizi S, Wu DC. Successful Treatment of Under-Eye Pigmentation in Skin Type IV with a Picosecond Alexandrite Laser with Diffractive Lens Array. *Dermatol Surg.* 2017;43(8):1095-1097.

20. Lee JW, Kim DS, Park CO. Circumscribed palmoplantar hypokeratosis: successful treatment with the 10 600-nm carbon dioxide fractional laser. *J Eur Acad Dermatol Venereol*. 2017;31(10):e473-e474.

21. Alavi S, Abolhasani E, Asadi S, Nilforoushzadeh M. Combination of Q-switched Nd: YAG and fractional erbium: YAG lasers in treatment of melasma: A randomized controlled clinical trial . *J Lasers Med Sci.* 2017;8(1):1–6.

22. Piccolo D, Kostaki D, Del Duca E, Cannarozzo G, Sannino M, Nisticò S. Long-Pulsed 1064-nm Nd:YAG Laser for the Treatment of Onychomycosis. *Photomed Laser Surg.* 2017;35(4):213–6.

23. Kelati A, Lagrange S, Le Duff F, Lacour JP, Passeron T. Treatment of elastosis perforans serpiginosa using a fractional carbon dioxide laser. *JAMA Dermatology.* 2017;153(10):1063–4.

24. Issler-Fisher AC, Fisher OM, Smialkowski AO, Li F, van Schalkwyk CP, Haertsch P, et al. Ablative fractional CO2laser for burn scar reconstruction: An extensive subjective and objective short-term outcome analysis of a prospective treatment cohort. *Burns*. 2017;43(3):573–82.

25. Vanarase M, Gautam RK, Arora P, Bajaj S, Meena N, Khurana A. Comparison of Q-switched Nd:YAG laser alone versus its combination with ultrapulse CO2 laser for the treatment of black tattoo. *J Cosmet Laser Ther.* 2017;19(5):259–65.

26. Bae YSC, Ng E, Geronemus RG. Successful treatment of two pediatric port wine stains in darker skin types using 595 nm laser. *Lasers Surg Med*. 2016;48(4):339–42.

27. Radmanesh M, Omidian E. The pulsed dye laser is more effective and rapidly acting than intralesional meglumine antimoniate therapy for cutaneous leishmaniasis. *J Dermatolog Treat*. 2017;28(5):422–5.

28. Osman MAR, Shokeir HA, Fawzy MM. Fractional erbium-doped yttrium aluminum garnet laser versus microneedling in treatment of atrophic acne scars: A randomized split-face clinical study. *Dermatologic Surg.* 2017;43:S47–56.

29. Lee SJ, Seok J, Park KY, Seo SJ. 755-nm Q-Switched Alexandrite Laser as a Treatment for Melanonychia Caused by Onychomycosis. *Dermatol Surg.* 2017 Jul;43(7):996-999.

30. Kim JY, Lee JW, Chung KY. Periorbital Syringomas Treated with an Externally Used 1,444 nm Neodymium-Doped Yttrium Aluminum Garnet Laser. *Dermatologic Surg.* 2017;43(3):381–8.

31. Strand M, Bergqvist G, Griffith S, Bergqvist E. The effect of recurrent pulsed dye laser treatments in rosacea patients. *J Cosmet Laser Ther.* 2017;19(3):160–4.

32. Soriano LF, Piansay-Soriano ME. Treatment of cutaneous larva migrans with a single session of carbon dioxide laser: a study of ten cases in the Philippines. *J Cosmet Dermatol*. 2017;16(1).

33. Kim S-J, Lee Y, Seo Y-J, Lee J-H, Im M. Comparative Efficacy of Radiofrequency and Pulsed Dye Laser in the Treatment of Rosacea. *Dermatol Surg.* 2017;43(2):204–9.

34. Yuan J, Chen H, Yan R, Cui S, Li YH, Wu Y, et al. Fractional CO2lasers contribute to the treatment of stable non-segmental vitiligo. E*ur J Dermatology.* 2016;26(6):592–8.

35. Osman MAR, Kassab AN. Carbon dioxide laser versus erbium:YAG laser in treatment of epidermal verrucous nevus: a comparative randomized clinical study. *J Dermatolog Treat.* 2017;28(5):452–7.

36. Shin YS, Cho EB, Park EJ, Kim KH, Kim KJ. A comparative study of pulsed dye laser versus long pulsed Nd:YAG laser treatment in recalcitrant viral warts. *J Dermatolog Treat.* 2017;28(5):411–6.

37. Kang HJ, Na JI, Lee JH, Roh MR, Ko JY, Chang SE. Postinflammatory hyperpigmentation associated with treatment of solar lentigines using a Q-Switched 532-nm Nd: YAG laser: a multicenter survey. *J Dermatolog Treat.* 2017;28(5):447–51.

38. Alshami MA, Mohana MJ, Alshami AM. Long-pulsed 532-Nm neodymium-doped yttrium aluminium garnet laser for treatment of facial plane warts in 160 yemeni patients. *Dermatologic Surg.* 2016;42(11):1273–8.

39. Karsai S, Jäger M, Oesterhelt A, Weiss C, Schneider SW, Jünger M, et al. Treating onychomycosis with the short-pulsed 1064-nm-Nd:YAG laser: results of a prospective randomized controlled trial. *J Eur Acad Dermatology Venereol.* 2017;31(1):175–80.

40. Shalaby SM, Bosseila M, Fawzy MM, Abdel Halim DM, Sayed SS, Allam RSHM. Fractional carbon dioxide laser versus low-dose UVA-1 phototherapy for treatment of localized scleroderma: a clinical and immunohistochemical randomized controlled study. *Lasers Med Sci.* 2016;31(8):1707–15.

41. Lee MK, Min KS, Park EJ, Kim KH, Kim KJ. A retrospective analysis of the treatment of melasma using a fractional long-pulsed alexandrite laser in Korean patients. *Dermatologic Surg.* 2016;42(8):952–60.

42. Yue B, Yang Q, Xu J, Lu Z. Efficacy and safety of fractional Q-switched 1064-nm neodymium-doped yttrium aluminum garnet laser in the treatment of melasma in Chinese patients. *Lasers Med Sci.* 2016;31(8):1657–63.

43. Zeng Y, Ji C, Zhan K, Weng W. Treatment of nasal ala nodular congenital melanocytic naevus with carbon dioxide laser and Q-switched Nd:YAG laser. *Lasers Med Sci.* 2016;31(8):1627–32.

44. Tian WCBA. Novel technique to treat melasma in Chinese: The combination of 2940-nm fractional Er:YAG and 1064-nm Q-switched Nd:YAG laser. *J Cosmet Laser Ther.* 2016;18(2):72–4.

45. Vachiramon V, Sirithanabadeekul P, Sahawatwong S. Low-fluence Q-switched Nd: YAG 1064-nm laser and intense pulsed light for the treatment of melasma. *J Eur Acad Dermatology Venereol.* 2015;29(7):1339–46.

46. Han HH, Lee JY, Rhie JW. Successful treatment of areolar Fox-Fordyce disease with surgical excision and 1550-nm fractionated erbium glass laser. *Int Wound J.* 2016 Oct;13(5):1016-9.

47. Balaraman B, Friedman PM. Hypertrichotic Becker's nevi treated with combination 1,550 nm non-ablative fractional photothermolysis and laser hair removal. *Lasers Surg Med.* 2016;48(4):350–3.

48. Fremlin GA, Szczecinska W, Maheshwari M, Abdullah A. Improvement of hyperpigmentation within a plexiform neurofibroma after treatment with Q-switched neodymium:yttrium-aluminium-garnet laser. *Clin Exp Dermatol.* 2016;41(3):336-7.

49. Shroff A, Malajian D, Czarnowicki T, Rose S, Bernstein DM, Singer GK, et al. Use of 308 nm excimer laser for the treatment of chronic hand and foot eczema. *Int J Dermatol.* 2016;55(8):e447–53.

50. Tartar D, Konia T, Fung M, Jagdeo J. Treatment of cutaneous angioimmunoblastic t-cell lymphoma with fractionated carbon dioxide laser. *Dermatologic Surg.* 2016;42(4):560–2.

51. Ali FR, Bakkour W, Ferguson JE, Madan V. Carbon dioxide laser ablation of dermatosis papulosa nigra: high satisfaction and few complications in patients with pigmented skin. L*asers Med Sci.* 2016;31(3):593–5.

52. Liu Y, Zeng W, Hu D, Jha S, Ge Q, Geng S, et al. The long-term effect of 1550 nm erbium:glass fractional laser in acne vulgaris. *Lasers Med Sci.* 2016;31(3):453–7.

53. Baumgartner J, Šimaljaková M, Babál P. Extensive angiokeratoma circumscriptum - successful treatment with 595-nm variable-pulse pulsed dye laser and 755-nm long-pulse pulsed alexandrite laser. *J Cosmet Laser Ther.* 2016;18(3):134–7.

54. Moore M, Mishra V, Friedmann DP, Goldman MP. Minocycline-Induced Postsclerotherapy Pigmentation Successfully Treated With a Picosecond Alexandrite Laser. *Dermatol Surg.* 2016;42(1):133–4.

55. Penev, Bakardzhiev, Chokoeva, Wollina T. Disseminated trichoblastomas - successfull treatment with CO2 laser. J *Eur Acad Dermatol Venereol.* 2016;30(12):e219-e220.

56. Kauvar ANB, Keaney TC, Alster T. Laser treatment of professional tattoos with a 1064/532-nm dual-wavelength picosecond laser. *Dermatologic Surg.* 2017;43(12):1434–40.

57. Noh TK, Chung BY, Yeo UC, Chang SY, Lee MW, Chang SE. Q-switched 660-nm versus 532-nm Nd:YAG laser for the treatment for facial lentigines in asian patients: A prospective, randomized, double-blinded, split-face comparison pilot study. *Dermatologic Surg.* 2015;41(12):1389–95.

58. Zeng Y, Zhan K, Xie WL, Lin QZ. Angiokeratoma of Fordyce response to long pulsed Nd:YAG laser treatment. *Dermatol Ther.* 2016;29(1):48–51.

59. Basnett A, Nguyen TA, Cannavino C, Krakowski AC. Ablative fractional laser resurfacing with topical paromomycin as adjunctive treatment for a recalcitrant cutaneous leishmaniasis wound. *Lasers Surg Med.* 2015;47(10):788–91.

60. Rodrigues M, Bekhor P. Treatment of minocycline-induced cutaneous pigmentation with the picosecond alexandrite (755-nm) laser. *Dermatologic Surg.* 2015;41(10):1179–82.

61. Ibrahim SM. Pulsed dye laser versus long pulsed Nd:YAG laser in the treatment of angiokeratoma of Fordyce: A randomized, comparative, observer-blinded study. *J Dermatolog Treat.* 2016;27(3):270–4.

62. Henes M, Vogt B, Neis F, Rall K, Litzenburger T, Wallwiener D, et al. Application of a Thulium Laser for Treatment of Cervical Neoplasias and Condylomas: A Feasibility Study. *Photomed Laser Surg.* 2015;33(9):481–5.

63. Chen YT, Shih PY, Chen HJ, Chen TJ. Treatment of axillary osmidrosis: A comparison between subcutaneous laser and superficial liposuction curettage. *J Eur Acad Dermatology Venereol.* 2015;29(10):2019–23.

64. Rivers JK, Rivers CA, Li MK, Martinka M. Laser therapy for an acquired glomuvenous malformation (Glomus Tumour): A nonsurgical approach. *J Cutan Med Surg.* 2016;20(1):80–3.

65. Kim HR, Ha JM, Park MS, Lee Y, Seo YJ, Kim CD, et al. A low-fluence 1064-nm Q-switched neodymium-doped yttrium aluminium garnet laser for the treatment of café-au-lait macules. *J Am Acad Dermatol.* 2015;73(3):477–83.

66. Ge Y, Jia G, Lin T. Gütegeschaltete Nd:YAG-Laserbehandlung labialer Lentigines bei Peutz-Jeghers-Syndrom. JDDG - *J Ger Soc Dermatology.* 2015;13(6):551–5.

67. Rodríguez-Ruiz M, Tellado MG, del Pozo Losada J. Combination of pulsed dye laser and propranolol in the treatment of ulcerated infantile haemangioma. *An Pediatría.* 2016;84(2):92–6.

68. Lloyd AA, Graves MS, Ross E V. Cutaneous siderosis secondary to intramuscular iron dextran treated with 755 nm Q-switched alexandrite laser: A case report. *Lasers Surg Med.* 2015;47(5):386–7.

69. Wen X, Li Y, Jiang X. A randomized, split-face clinical trial of Q-switched alexandrite laser versus Q-switched Nd:YAG laser in the treatment of bilateral nevus of Ota. *J Cosmet Laser Ther.* 2016;18(1):12–5.

70. Zhong SX, Tao YC, Zhou JF, Liu YY, Yao L, Li SS. Infantile hemangioma: Clinical characteristics and efficacy of treatment with the long-pulsed 1,064-nm neodymium-doped yttrium aluminum garnet laser in 794 Chinese patients. *Pediatr Dermatol.* 2015;32(4):495–500.

71. SS ESMHH. Efficacy of different modes of fractional CO2 laser in the treatment of primary cutaneous amyloidosis: A randomized clinical trial. *Lasers Surg Med.* 2015;47(5):388–95.

72. Phillips TJ, Morton LM, Uebelhoer NS, Dover JS. Ablative fractional carbon dioxide laser in the treatment of chronic, posttraumatic, lower-extremity ulcers in elderly patients. *JAMA Dermatology.* 2015;151(8):868–71.

73. Alabdulrazzaq H, Brauer JA, Bae YS, Geronemus RG. Clearance of yellow tattoo ink with a novel 532-nm picosecond laser. *Lasers Surg Med.* 2015;47(4):285–8.

74. Gurel MS, Aral BB. Effectiveness of erbium:YAG laser and cryosurgery in seborrheic keratoses: Randomized, prospective intraindividual comparison study. *J Dermatolog Treat.* 2015;26(5):477–80.

75. Vachiramon V1, Anusaksathien P1, Kanokrungsee S1, Chanprapaph K1Fractional Carbon Dioxide Laser for Keratosis Pilaris: A Single-Blind, Randomized, Comparative Study. *Biomed Res Int.* 2016;2016:1928540.

76. Lee SE, Choi JY, Hong KT, Lee KR. Treatment of acquired and small congenital melanocytic nevi with combined Er:YAG laser and long-pulsed alexandrite laser in asian skin. *Dermatologic Surg.* 2015;41(4):473–80.

77. El-Tatawy RA, Abd El-Naby NM, El-Hawary EE, Talaat RAZ. A comparative clinical and mycological study of Nd-YAG laser versus topical terbinafine in the treatment of onychomycosis. *J Dermatolog Treat.* 2015;26(5):461–4.

78. Ortiz AE, Anderson RR, Avram MM. 1064nm Long-pulsed Nd:YAG laser treatment of basal cell carcinoma. *Lasers Surg Med.* 2015;47(2):106–10.

79. Campuzano-García AE, Torres-Alvarez B, Hernández-Blanco D, Castanedo-Cázares JP. Hailey-Hailey disease improved by fractional CO2 laser. *J Cosmet Laser Ther.* 2015;17(4):213–5.

80. Alsenaid A, Prinz JC. Inadvertent pregnancy during ustekinumab therapy in a patient with plaque psoriasis and impetigo herpetiformis. *J Eur Acad Dermatology Venereol.* 2016;30(3):488–90.

81. Goldberg DJ, Beckford AN, Mourin A. Verruca vulgaris: Novel treatment with a 1064 nm Nd:YAG laser. *J Cosmet Laser Ther.* 2015;17(2):116–9.

82. Korkmaz Ş, Ekici F, Sül S. Argon laser-assisted treatment of benign eyelid lesions. *Lasers Med Sci.* 2015;30(2):527–31.

83. Krakowski AC, Feldstein S, Shumaker PR. Successful treatment of pearly penile papules with carbon dioxide laser resurfacing after local anesthesia in an adolescent patient. *Pediatr Dermatol.* 2015;32(3):433–5.

84. Goo BL, Kang JS, Cho S Bin. Treatment of early-stage erythematotelangiectatic rosacea with a Q-switched 595-nm Nd:YAG laser. *J Cosmet Laser Ther.* 2015;17(3):139–42.

85. Su Q, Lin T, Wu Q, Wu Y, Guo L, Ge Y. Efficacy of 595nm pulsed dye laser therapy for Mibelli angiokeratoma. *J Cosmet Laser Ther.* 2015;17(4):209–12.

86. Shi W, Wang J, Lin Y, Geng J, Wang H, Gong Y, et al. Treatment of port wine stains with pulsed dye laser: A retrospective study of 848 cases in shandong province, People's Republic of China. *Drug Des Devel Ther.* 2014;8:2531–8.

87. Brauer A.B, Correa LM, Bernstein L, Hale EK, Karen J, Brightman LA, et al. Evaluation of a picosecond 755nm alexandrite laser and defractive lens array for scarring. *Lasers in Surg Med.* 2013. Lasers in Surgery and Medicine. 2013;45:15-15.

88. Ibrahim O, Khan M, Bolotin D, Dubina M, Nodzenski M, Disphanurat W, et al. Treatment of keratosis pilaris with 810-nm diode laser a randomized clinical trial. *JAMA Dermatology.* 2015;151(2):187–91.

89. Moneib H, Tawfik AA, Youssef SS, Fawzy MM. Randomized split-face controlled study to evaluate 1550-nm fractionated erbium glass laser for treatment of acne vulgaris-an image analysis evaluation. *Dermatologic Surg.* 2014;40(11):1191–200.

90. Yun WJ, Lee SM, Han JS, Lee SH, Chang SY, Haw S, et al. A prospective, split-face, randomized study of the efficacy and safety of a novel fractionated intense pulsed light treatment for melasma in Asians. *J Cosmet Laser Ther.* 2015;17(5):259–66.

91. Smith EA, Patel SB, Whiteley MS. Evaluating the success of Nd: YAG laser ablation in the treatment of recalcitrant verruca plantaris and a cautionary note about local anaesthesia on the plantar aspect of the foot. *J Eur Acad Dermatology Venereol.* 2015;29(3):463–7.

92. Hélou J, Maatouk I, Obeid G, Moutran R, Stéphan F, Tomb R. Fractional laser for vitiligo treated by 10 600 nm ablative fractional carbon dioxide laser followed by sun exposure. Lasers Surg Med. 2014;46(6):443–8.

93. Thomas CL, Kim B, Lam J, Richards S, See A, Kalouche S, et al. Objective severity does not capture the impact of rosacea, acne scarring and photoaging in patients seeking laser therapy. J *Eur Acad Dermatology Venereol.* 2017;31(2):361–6.

94. Kaune KM, Lauerer P, Kietz S et al. Combination therapy of infantile hemangiomas with pulsed dye laser and Nd:YAG laser is effective and safe. *J Dtsch Dermatol Ges* 2014; 12: 473–478

95. Han XD, Goh CL. A case of lichen planus pigmentosus that was recalcitrant to topical treatment responding to pigment laser treatment. *Dermatol Ther.* 2014;27(5):264–7.

96. Deaver D, Cauthen A, Cohen G, Sokol L, Glass F. Excimer laser in the treatment of mycosis fungoides. *J Am Acad Dermatol.* 2014;70(6):1058–60.

97. Eimpunth S, Wanitphakdeedecha R, Triwongwaranat D, Varothai S, Manuskiatti W. Therapeutic outcome of melasma treatment by dual-wavelength (511 and 578 nm) laser in patients with skin phototypes III-V. *Clin Exp Dermatol.* 2014 Apr;39(3):292-7.

98. Dinsdale G, Murray A, Moore T, Ferguson J, Wilkinson J, Richards H, et al. A comparison of intense pulsed light and laser treatment of telangiectases in patients with systemic sclerosis: A within-subject randomized trial. R*heumatol (United Kingdom).* 2014;53(8):1422–30.

99. Ma G, Wu P, Lin X, Chen H, Li W, Hu X, et al. Nd: YAG laser for "fractional" treatment of angiofibromas. *Int J Dermatol.* 2014;53(5):638–42.

100. Kimura U, Takeuchi K, Kinoshita A, Takamori K, Suga Y. Long-pulsed 1064-nm neodymium:yttrium-aluminum-garnet laser treatment for refractory warts on hands and feet. *J Dermatol.* 2014;41(3):252–7.

101. AlGhamdi KM. Successful Treatment of Atrophic Scars from Cutaneous Leishmaniasis Using a Fractional Laser. *J Cutan Med Surg.* 2010;14(6):303-6.

102. Lekakh O, Mahoney AM, Novice K, Kamalpour J, Sadeghian A, Mondo D, et al. Treatment of acne vulgaris with salicylic acid chemical peel and pulsed dye laser: A split face, rater-blinded, randomized controlled trial. *J Lasers Med Sci.* 2015;6(4):167-70.

103. Beleznay K, Friedmann DP, Liolios AM, Perry A, Goldman MP. Lupus miliaris disseminatus faciei treated with 1,565nm nonablative fractionated laser resurfacing: A case report. Lasers *Surg Med.* 2014;46(9):663-5.

104. Sajan JA, Tibesar R, Jabbour N, Lander T, Hilger P, Sidman J. Assessment of pulsed-dye laser therapy for pediatric cutaneous vascular anomalies. *JAMA Facial Plast Surg.* 2013;15(6):434–8.

105. Kutlubay Z, Yardimci G, Gokler G, Engin B. A dystrophic calcinosis cutis case treated with CO2 laser. *J Cosmet Laser Ther.* 2014;16(3):144-6.

106. Gungor S, Gokdemir G, Sayilgan T, Ozcan D. Evaluation of an ablative and non-ablative laser procedure in the treatment of striae distensae. *Indian J Dermatol Venereol Leprol.* 2014;80(5):409-12.

107. Lee SJ, Chung WS, Lee JD, Kim HS. A patient with cupping-related post-inflammatory hyperpigmentation successfully treated with a 1,927 nm thulium fiber fractional laser. *J Cosmet Laser Ther.* 2014;16(2):66-8.

108. Lee MC, Chang CS, Huang YL, Chang SL, Chang CH, Lin YF, et al. Treatment of melasma with mixed parameters of 1,064-nm Q-switched Nd:YAG laser toning and an enhanced effect of ultrasonic application of vitamin C: a split-face study. *Lasers Med Sci.* 2015;30(1):159-63.

109. Bencini PL, Tourlaki A, Galimberti M, Pellacani G. Non-ablative fractionated laser skin resurfacing for the treatment of aged neck skin. *J Dermatolog Treat.* 2015;26(3):252-6.

110. Zeng Y, Li XQ, Lin QZ, Zhan K. Treatment of angiokeratoma of Mibelli alone or in combination with pulsed dye laser and long-pulsed Nd: YAG laser. D*ermatol Ther.*2014;27(6):348-51.

111. Kim YK, Kim DY, Lee SJ, Chung WS, Cho SB. Therapeutic efficacy of long-pulsed 755-nm alexandrite laser for seborrheic keratoses. *J Eur Acad Dermatology Venereol.* 2014;28(8):1007–11.

112. Biondo G, Greco S, Mavilia L, Mercuri SR. Treatment of nodular facial angiofibromas in tuberous sclerosis, using ultrapulse carbon dioxide laser. *Clin Exp Dermatol.* 2014;39(6):738-40.

113. Joo J, Fung MA, Jagdeo J. Successful treatment of scrotal verruciform xanthoma with shave debulking and fractionated carbon dioxide laser therapy. *Dermatol Surg.* 2014;40(2):214-7.

114. Hammami Ghorbel H, Lacour JP, Passeron T. Successful treatment with 532-nm Q-switched Nd:YAG laser of cutaneous siderosis following intravenous iron extravasation. *J Eur Acad Dermatol Venereol.* 2015;29(4):818-9.

115. Bjørn M, Stausbøl-Grøn B, Braae Olesen A, Hedelund L. Treatment of acne scars with fractional CO2 laser at 1-month versus 3-month intervals: An intra-individual randomized controlled trial. *Lasers Surg Med.* 2014;46(2):89-93.

116. Salas-Alanis JC, Lopez-Cepeda LD, Elizondo-Rodriguez A, Morales-Barrera ME, Ramos-Garibay AR. Hypertrichosis lanuginosa congenita treated with diode laser epilation during infancy. P*ediatr Dermatol.* 2014;31(4):529-30.

117. Shin J, Kim M, Park SH, Oh SH. The effect of fractional carbon dioxide lasers on idiopathic guttate hypomelanosis: A preliminary study. *J Eur Acad Dermatol Venereol.* 2013;27(2):e243-6.

118. Pickert AJ, Carpentieri D, Price H, Hansen RC. Early morphea mimicking acquired port-wine stain. *Pediatr Dermatol. Pediatr Dermatol.* 2014;31(5):591-4.

119. Zeng Y, Zheng YQ. Successful treatment of congenital melanocytic nevus on tragus with CO2 laser. *J Dermatolog Treat.* 2014;25(4):287-9.

120. Zeng Y. Divided nevus of the eyelid: Successful treatment with CO2 laser. J Dermatolog Treat. 2014; *J Dermatolog Treat.* 2014;25(4):358-9.

121. Alcántara-González J, Boixeda P, Pérez-García B, Truchuelo-Díez MT, González-Muñoz P, Jaén-Olasolo P. Venous malformations treated with dual wavelength 595 and 1064 nm laser system. *J Eur Acad Dermatol Venereol.* 2013;27(6):727-33.

122. Richard A, Chevalier JM, Verneuil L, Sergent B, Tesnière A, Dolfus C, et al. Traitement des cylindromes cutanés par laser CO2 dans le syndrome de Brooke-Spiegler. *Ann Dermatol Venereol.*2014;141(5):346-53.

123. Alcántara-González J, Boixeda P, Truchuelo-Díez MT, Pérez-García B, Alonso-Castro L, Jaén Olasolo P. Infantile Hemangiomas Treated by Sequential Application of Pulsed Dye Laser and Nd:YAG Laser Radiation: A Retrospective Study. *Actas Dermosifiliogr.* 2013;104(6):504-11.

124. Norisugi O, Yamakoshi T, Shimizu T. Successful treatment of lichen amyloidosis using a CO2 surgical laser. *Dermatol Ther.* 2014r;27(2):71-3.

125. Lapidoth M, Adatto M, Halachmi S. Treatment of actinic keratoses and photodamage with non-contact fractional 1540-nm laser quasi-ablation: An ex vivo and clinical evaluation. *Lasers Med Sci.* 2013;28(2):537-42.

126. Tenna S, Filoni A, Pagliarello C, Paradisi M, Persichetti P. Eyelid milia en plaque: A treatment challenge with a new CO2 fractional laser. *Dermatol Ther.* 2014;27(2):65-7.

127. Cameli N, Mariano M, Serio M, Ardigò M. Preliminary comparison of fractional laser with fractional laser plus radiofrequency for the treatment of acne scars and photoaging. *Dermatol Surg.* 2014;40(5):553-61.

128. Marmon S, Shek SYN, Yeung CK, Chan NPY, Chan JC, Chan HHL. Evaluating the safety and efficacy of the 1,440-nm laser in the treatment of photodamage in Asian skin. *Lasers Surg Med.* 2014;46(5):375-9.

129. Saelim P, Pongprutthipan M, Pootongkam S, Jariyasethavong V, Asawanonda P. Long-pulsed 1064-nm Nd:YAG laser significantly improves keratosis pilaris: A randomized, evaluator-blind study. *J Dermatolog Treat.* 2013;24(4):318-22.

130. Grillo E, Boixeda P, Ballester A, Miguel-Morrondo A, Truchuelo T, Jaén P. Pulsed dye laser treatment for facial flat warts. *Dermatol Ther.*2014;27(1):31-5.

131. Becher GL, Cameron H, Moseley H. Treatment of superficial vascular lesions with the KTP 532-nm laser: Experience with 647 patients. *Lasers Med Sci.* 2014;29(1):267-71.

132. Su W, Ke Y, Xue J. Beneficial effects of early treatment of infantile hemangiomas with a long-pulse Alexandrite laser. *Lasers Surg Med.* 2014;46(3):173-9.

133. Fioramonti , De Santo L, Ruggieri M, Carella S, Federico LT, Onesti MG, Scuderi N et al. Co2/ Erbium:YAG/Dye laser combination: an effective and successful treatment for angiofibromas in tuberous sclerosis. *Aesthetic Plast Surg.* 2014;38(1):192-198.

134. Nguyen T V., Becker EM, Miller WA, Browning JC. Plaque-type glomuvenous malformations successfully treated using combined pulsed dye laser and neodymium-doped yttrium aluminum garnet laser. *Dermatol Surg.* 2014;40(1):89-92.

135. Emer J, Uslu U, Waldorf H. Improvement in lupus pernio with the successive use of pulsed dye laser and nonablative fractional resurfacing. *Dermatol Surg.* 2014;40(2):201-2.

136. Hilton S, Heise H, Buhren BA, Schrumpf H, Bölke E, Gerber PA. Treatment of melasma in Caucasian patients using a novel 694-nm Q-switched ruby fractional laser. *Eur J Med Res.* 2013;14;18:43

137. Yélamos O, Roé E, Baselga E, Puig L. Pediatric cutaneous lupus erythematosus treated with pulsed dye laser. *Pediatr Dermatol.* 2014;31(1):113-5.

138. Kriechbaumer LK, Susani M, Kircher SG, Distelmaier K, Happak W. Comparative study of CO2- and Er:YAG laser ablation of multiple cutaneous neurofibromas in von Recklinghausen's disease. *Lasers Med Sci.* 2014;29(3):1083-91.

139. Niwa Massaki AB, Eimpunth S, Fabi SG, Guiha I, Groff W, Fitzpatrick R.Treatment of melasma with the 1,927-nm fractional thulium fiber laser: A retrospective analysis of 20 cases with long-term follow-up. *Lasers Surg Med*. 2013;45(2):95-101.

140. Bruscino N, Conti R, Campolmi P, Bonan P, Cannarozzo G, Lazzeri L, et al. Dermatosis Papulosa Nigra and 10,600-nm CO2 laser, a good choice. *J Cosmet Laser Ther.* 2014;16(3):114-6.

141. Alshami MA. Long-pulsed 532-nm Nd:YAG laser treatment for small acquired melanocytic nevi in a single session: An 8-year study on 350 Yemeni patients. *J Cosmet Laser Ther.* 2014;16(1):14-20.

142. Serowka KL, Saedi N, Dover JS, Zachary CB. Fractionated ablative carbon dioxide laser for the treatment of rhinophyma. *Lasers Surg Med*. 2014;46(1):8-12.

143. Naouri M, Mazer J-M. Finger onychomycosis due to Candida tropicalis: short-pulsed Nd:YAG laser therapy. *Ann Dermatol Venereol.* 2013;140(10):610-3.

144. Kavoussi H, Ebrahimi A, Rezaei M. Treatment and cosmetic outcome of superpulsed C02laser for basal cell carcinoma. *Acta Dermatovenerol Alp Pannonica Adriat*. 2013 Sep;22(3):57-61.

145. Van Drooge AM, Bosveld B, Van Der Veen JPW, De Rie MA, Wolkerstorfer A. Long-pulsed 1064 nm Nd:YAG laser improves hypertrophic port-wine stains. *J Eur Acad Dermatol Venereol.* 2013;27(11):1381-6.

146. Conti R, Bassi A, Lorenzoni E, Bruscino N, Scatena C, Bonan P, et al. Jessner-Kanof disease: Two effective and sure therapeutic options. *Dermatol Ther.* 2013;26(4):373-6.

147. Polder KD, Mithani A, Harrison A, Bruce S. Treatment of macular seborrheic keratoses using a novel 1927-nm fractional thulium fiber laser. *Dermatol Surg.* 2012l;38(7 Pt 1):1025-31.

148. Choi CW, Kim HJ, Lee HJ, Kim YH, Kim WS. Treatment of nevus of Ota using low fluence Q-switched Nd: YAG laser. *Int J Dermatol.* 2014;53(7):861-5.

149. Shumaker PR, Dela Rosa KM, Krakowski A. Treatment of lymphangioma circumscriptum using fractional carbon dioxide laser ablation. *Pediatr Dermatol.* 2013 ;30(5):584-6.

150. Halachmi S, Israeli H, Ben-Amitai D, Lapidoth M. Treatment of the skin manifestations of hereditary hemorrhagic telangiectasia with pulsed dye laser. *Lasers Med Sci.* 2014;29(1):321–4.

Supplemental table 2. Outcomes identified in laser studies[2] assigned to outcome domains

Domain	Outcomes	Frequency studies reporting outcome
Appearance (77%)	Clinical improvement (1-6,8,9,11,13,15,18-26,28-31,34,37,39,41,42,44,45,48,53,57,58,63,68,70,71,73, 75,76,77,79,80,84,85,87-90,95-99,103,104,107,109, 110,115,117,119,121,122,124-127,129,130,133,134, 136,137-139,142,143,146,150)	83 (55%)
	Clearance (2,4,7,11,19,27,36,38,42,47,50,54,56,60,61,73,77, 78,83,86,100, 102,114,144,149)	25 (17%)
	Cure/healing (14,59,62,67,72,74,82,110)	7 (5%)
	Overall response (7,35,39,41,76,78,101)	7 (5%)
	Reduction (16,52,53,71,81,89,116)	7 (5%)
	Lightening of lesion (48,108)	2 (1%)
	Resolution (118, 121)	2 (1%)
Long term effects (23%)	Relapse (9,16,62,79)	4 (3%)
	Recurrence (6,7,11,12,15,16,20,27,32,35,42,43, 46,50,51,53, 64,65,67,71,80,83,87,105,113,121,136,139,140,145)	30 (20%)
	Reappearance (138)	1 (1%)
Physical signs assessed by observer (37%)	Skin thickness (17,19,40,104,106,121,141,145)	8 (5%)
	Skin roughness (17,88,102,121,129)	5 (3%)
	Erythema (3,5,8,13,20,21,26,37,40,42,56,88,90,106, 111,129,135,147,148)	19 (13%)
	Atrophy (12,40,101,115,122)	5 (3%)
	Induration (12,27,135)	3 (2%)
	Scars (10,17,24,43,115,122,126,132,141,142,144,147,145)	13 (9%)
	Scaling (49,111,147)	3 (2%)
	Vesiculation (49)	1(1%)
	Edema (49,127,131,132,142)	5 (3%)
	Fissures (49)	1(1%)
	Pruritus (3,49,124)	3 (2%)
	Melanin (5,6,21,42,90,97)	6 (4%)
	Depigmentation (43)	1(1%)
	Repigmentation (92)	1(1%)
	Color (13,21,94,104,121)	5 (3%)
	Blanching rate (13,27)	2 (1%)
	Mean hair density (3)	1 (1%)

2 For references, see supplemental table 1

Supplemental table 2. Outcomes identified in laser studies assigned to outcome domains

Domain	Outcomes	Frequency studies reporting outcome
	Changes in hair-follicle phase and hair-shaft diameter (3)	1 (1%)
	Chromonychia (22)	1 (1%)
	Onycholysis (22)	1 (1%)
	Longitudinal striae (22)	1 (1%)
	Jagged proximal edge (22)	1 (1%)
	Hyperkeratotic changes (22,29,49)	3 (2%)
	Overall clinical improvement of nails (39)	1 (1%)
	Dry skin (3)	1 (1%)
	Seborrheic dermatitis (3)	1 (1%)
	Size (3,37,104,123)	4 (3%)
	Degree of vascularization (123)	1 (1%)
Physical signs assessed by patients (13%)	Patients self-assessment of melasma (97,41,42,108,139)	5 (3%)
	State of disease (93)	1 (1%)
	Severity of disease (93)	1 (1%)
	Improvement (64,75,98,102)	4 (3%)
	Dry skin (33)	1 (1%)
	Irritation (33)	1 (1%)
	Pruritus (32, 46)	2 (1%)
	Sun sensitivity (86)	1 (1%)
	Scarring opinion (17,115)	2 (1%)
	Breathing (112,121)	2 (1%)
	Vision (112,126)	2 (1%)
Pain (17%)	Pain/tolerability (6,15,28,30,34,39,42,45,47,49,56,57,62,63, 64,65,67,71,73,77,84,87,90, 115,122)	25 (17%)
Satisfaction (23%)	Satisfaction with improvement in overall appearance and texture (87)	1 (1%)
	Satisfaction with treatment (6,51)	2 (1%)
	Overall satisfaction (1,6,8,12,16,26,31,34,35,43,45,46,55,5 6,57,58,65,69,71,75,82,83,84,91,93,94,97,115,121,125,129)	32 (21%)
Health-related quality of life (HlQol) (3%)	Quality of life (17,24,48,93)	4 (3%)
Psychosocial Functioning (1%)	Anxiety and depression (98)	1(1%)
	Body image dissatisfaction and social discomfort related to appearance (98)	1(1%)

Supplemental table 2. Outcomes identified in laser studies assigned to outcome domains

Domain	Outcomes	Frequency studies reporting outcome
Adverse events (52%)	Skin irritation (62)	1 (1%)
	Sensitivity (11,5)	2 (1%)
	Pruritus (3,24,13,15,56,96)	6 (4%)
	Burning (8,20,34,39,41,42,45,62,75,90,96,97,98,116,117)	15 (10%)
	Permanent contracture (64)	1(1%)
	Paraesthesia (24,39,63)	3 (2%)
	Rash (86)	1 (1%)
	Itching (7,30,62)	3 (2%)
	Erythema (2,3,4,6,7,8,10,21,26,28,30,34,35,41,42,45,51,52,56, 66, 69,72,74,76,78,84,87,89,90,97,99,101,109,115,117,127,142)	37 (25%)
	Purpura or petechiae (8,25,26,27,41,78,85,114)	8 (5%)
	Bleeding, hemorrhage (7,11,3,25,61,62,111)	7 (5%)
	Haematoma, bruising (64,98,131)	3 (2%)
	Swelling , edema (2,3 4,7,6,11,26,34,39,41,42,51,61,78,84,99,107,109, 115)	18 (12%)
	Dryness (3,6,9)	3 (2%)
	Induration (12,63)	2 (1%)
	Scaling (4,6,51,69,97,109)	6 (4%)
	Vesicles, bullae (6,41,69)	3 (2%)
	Atrophy (12,84,104)	3 (2%)
	Crusting (1,4,8,26,30,34,51,56, 61,66,69,97,99,100,111,114)	16 (11%)
	Blistering (1,4,6,8,10,25,26,39,72,78,94,100,111,123)	14 (9%)
	Erosion (3,4,10,9,123)	5 (3%)
	Scabbing (26,131)	2 (1%)
	Desquamation (42)	1(1%)
	Scarring/ residual scar (1,2,4,11,27,35,41,45,47,64,68,70,76 , 78,84,85,90,97,100,101,104,111,123,131)	24 (16%)
	Pigmentation (86)	1 (1%)
	Depigmentation (86,138)	2 (1%)
	Hyperpigmentation (2,6,7,27,44,50,65,70,75,78,88,101,108, 111,114, 115,129,131,138)	19 (13%)
	Post-inflammatory hyperpigmentation (2,6,7, 27,44,50,65, 70,75,78,88,101,107,117,137,139,141,146)	18 (12%)
	Hypopigmentation (1,2,6,8,11,19,35,41,45,47,50,51,65,68,69,71, 76,82,90,97,98,99,104,111,115,120,121,129,145)	29 (19%)

Supplemental table 2. Outcomes identified in laser studies assigned to outcome domains

Domain	Outcomes	Frequency studies reporting outcome
	Bacterial infection (11,38,45,64,71,74,101,111,123)	9 (6%)
	Viral infection (111,123)	2 (1%)
	Wounds (115)	1 (1%)
	Post-operative Necrosis (121)	1 (1%)
	Acneiform eruptions (11)	1 (1%)
	Milia (11)	1 (1%)
	Excessive granulation tissue (11)	1 (1%)
	Transient hair shedding (3)	1 (1%)
	Breakage of the hair shafts (3)	1 (1%)
	Dyspigmentation (53,111)	2 (1%)
	Texture change (53,70)	2 (1%)
	Pinpoint bleeding (56,101,114)	3 (2%)
	Post-operative ulcer (70,121,132)	3 (2%)
	Skin Peeling (75)	1 (1%)
	Guttate hypomelanosis (87)	1 (1%)
	First degree burn (90,96)	2 (1%)
	Darkening of melasma (97)	1 (1%)

Supplemental table 3. Outcome measurement instruments reported to measure domains[3]

Outcome measurement instruments used to measure domains of appearance and long-term effects, with details	Frequency
Instruments	
Clinical assessment (4-9,11,12,14,17,20,22,23,25,39,40,47,48,53,54,69,71,72,73,77,81,102,109,129)	29 (19%)
Double blind assessment of before and after photographs (1-3,6,7,8,10,26,28,30,34,35,37,38,41,42,45,56,57,61,65,66,70,71,74-76,86,92,97-99, 104,111, 121,125,129,132,138,141,147,150)	42 (28%)
Photographs (32,44,52,88,96,100,106,108,128,130,131,133,148)	13 (9%)
Double blind clinical assessment (32,44,52,88,96,100)	6 (4%)
Dermoscopic evaluation (3,7,12,22,98)	5 (3%)
Dermoscopic microphotographs (35)	1 (1%)
Histopathological analysis (6,7,11,26,28,40,71,89,96,99,100,106,113)	13 (9%)
Mycological culture (77)	1 (1%)
Patient reported questionnaire (1,26,31,40,51,91)	6 (4%)
Patient assessment (6,8,34,42,57,145)	6 (4%)
Palpation (7)	1 (1%)
Mexameter (6,21,90)	3 (2%)
Chromameter (13)	1 (1%)
Modified melasma area and severity index (mMASI) (6,41,75,87,139)	5 (3%)
Melasma area and severity index (MASI) (42,90,136)	3 (2%)
Tattoo ink Lightening scale (8)	1 (1%)
Physicians global assessment scale (PGA) (42,49,52,76,145)	5 (3%)

3 For references, see supplemental table 1

Supplemental table 3. Outcome measurement instruments reported to measure domains

Vancouver scar scale (VSS) (17)	1 (1%)
Patient and observer scar assessment score (POSAS) (17)	1 (1%)
Modified total lesion/symptom score (mTLSS) (49)	1 (1%)
Visual analogue scale (VAS) (25,45,63,65,75,87,92,93,97,108,125,128)	12 (8%)
Melanin index (MI) (43,90)	2 (1%)
Erythema index (EI) (43,90)	2 (1%)
Pigmentation area and severity index (PSI) (57)	1 (1%)
Global assessment of the aesthetic improvement scale (GAIS)(57,84)	1 (1%)
Burton Acne scale (102)	1 (1%)
Imaging (17,21,42,40,57,89,75,84,109)	9 (6%)
Laser Doppler Imaging (LDI) (98)	1 (1%)
Categorical	**83 (57%)**
Clearance of lesions, no clearance of lesions (4,9,16,7,11,19,26,38,47,54,56,60,74,80,83)	15 (10%)
Improvement, no improvement of lesions (6,13,18,19,20,21,24,25,26,29,31,37,44,48,58,68, 71,79,88,110,112)	21 (14%)
Reduction of lesion, no or partial reduction (23,35,52,53,55,71,81,95,96)	9 (6%)
Healing, no healing (6,14,27,38,58,59,62,67,72,8)	10 (7%)
Mild, moderate, severe (6,14,39,78,94)	5 (3%)
Excellent, good, fair or poor (7,12,22,106)	4 (3%)
Relapse, no relapse (9,62)	2 (1%)
Recurrence, no recurrence (6,11,12,15,20,32,43,46,50,51,53,64,67,82,83,87,95,96,140,146)	20 (13%)

Supplemental table 3. Outcome measurement instruments reported to measure domains

Ranking by grade	**37 (25%)**
Percentage quartile grading	
Grade 1 (<25%) , Grade 2 (25% to 50%) Grade 3: (51% to 75% improvement) and Grade 4 (>75% improvement) (1,8,28,41,66,70,71,73,76,87,111,117,121,125,129,141,147,148)	18 (12%)
Percentage quintile grading	
grade 1: poor (<25%), grade 2: fair (25–50%), grade 3: good (51–75%),grade 4: excellent 76–95%), and grade 5: clear (>96%) (25,56,130,133)	4 (3%)
grade 1: poor (<10% improvement); grade 2: slightly improved (>10%–25% improvement); grade 3, moderately improved (>25%–50% improvement); grade 4: good (>50%–75%improvement); and grade 5: excellent (>75% improvement) (57,89,90,102,104,129,150)	7 (5%) 2 (1%)
no or minimal (<25%; grade 1),moderate (25–49%; grade 2), marked (50–74%; grade 3), excellent (75–99%; grade 4), and complete (100%; grade 5) (5,92)	5 (3%)
Percentage sextile grading	
Grade 1, no change after laser treatment; Grade 2, mild improvement (1–25%clearing); Grade 3, some improvement (26–50% clearing); Grade 4, moderate improvement (51–75% clearing); Grade 5, significant improvement (76–99% clearing); and Grade 6, complete improvement (100% clearing). (61,69,108, 109,138)	1 (1%)
Percentage nine-tile grading	
grade −4, >75% worsening; grade −3, 51–75% worsening; grade −2, 26–50% worsening; grade −1, 1–25% worsening; grade 0, no change; grade 1, 1–25% improvement (minimal); grade 2, 26–50% improvement (moderate); grade 3, 51–75% improvement (good); grade 4, >75% improvement (excellent). (45)	

Supplemental table 3. Outcome measurement instruments reported to measure domains

Ranking by classification	**26 (17%)**
4-point scale:	
"poor" (0%–25% improvement), "fair" (26%–50% improvement), "good" (51%–75% improvement), or "excellent" (76%–100% improvement) (10,33,63)	3 (2%)
	1 (1%)
no improvement, fair: <40 %, good: 40–59 %, very good: ≥60 % improvement (40)	4 (3%)
No or minimal (<25%), moderate (25-49%), marked (50-74%), or excellent (≥75). (34,75,101,145)	3 (2%)
No improvement (≤25%), mild improvement (25–50%) %), moderate improvement (50–75%), and marked improvement (≥75) (77,85,99)	1 (1%)
	1 (1%)
5-point scale:	
"recurrent or worse," "poor" (0%–24% clearance), "fair" (25%–49% clearance), "good" (50%–74% clearance), and "excellent" (75%–100% clearance).(6)	2 (1%)
	3 (2%)
"poor to no response" (0–24%); "fair response" (25–49%); "good response" (50–74%); "excellent response" (75–99%) and complete response" (100% clearance). (36)	1 (1%)
"poor" (0-25% clearance), "fair" (26-50% clearance), "good" (51-75% clearance), "excellent" (76-95% clearance), and "complete" (96-100% clearance).(65, 100)	
worse than before" (score: – 1), "clinically unchanged" (score: 0), "slightly improved" (score: 1), "moderately improved" (score: 2), and "markedly improved" (score: 3) (3,84,131)	1 (1%)
–2 (appearance much worse at later time point) to +2 (appearance much better) (98)	2 (1%)
6-point scale:	
0 for no improvement, 1 for minimal (1%-25% clearance), 2 for fair (26%-50%), 3 for good (51%-75% clearance), 4 for excellent (76%-99% clearance), and 5 for complete clearance (100% clearance) (2)	1 (1%)
	1 (1%)
0 worsening; 1, no change; 2, mild (lesion clearance < 25 %); 3, moderate improvement (lesion clearance 25–50 %); 4, good (lesion clearance 50–75 %); and 5, remarkable (lesion clearance > 75 %) (42,129)	2 (1%)
-1 (worse than baseline), 0 (no improvement) 1 (< 25% improvement), 2 (25–50% improvement), 3 (51–75% improvement), or 4 (75% improvement) (97)	1 (1%)
7-point scale:	
Significant deterioration, –3 points; moderate deterioration, –2 points; slight deterioration, –1 point; no change, 0 points; slight improvement, +1 point; moderate improvement, +2 points; and significant improvement, +3 points.(3)	
10-point scale:	
Improvement grading on a 0 to 10–point scale according to appearance improvement from 0% to 100%. (30,128)	
Efficacy from 0 (0, absent) to 10 (10, worst possible) (15)	
Scale used to measure domain of satisfaction	Frequency

Supplemental table 3. Outcome measurement instruments reported to measure domains

Categorical	**16 (11%)**
satisfied, not satisfied (46,110,112 114,119,120)	6 (4%)
very satisfied, satisfied, moderately satisfied, slightly satisfied, or unsatisfied (6,56)	2 (1%)
not very satisfied, moderately satisfied, satisfied or very satisfied (35,117)	2 (1%)
very satisfied, satisfied, slightly satisfied, or unsatisfied (65,94)	2 (1%)
excellent, good, moderate, or poor (65,94)	2 (1%)
significant, moderate, mild, none (31)	1 (1%)
successful, partially successful, unsuccessful (91)	1 (1%)
Percentile ranking by classification	**8 (5%)**
3 -point scale	
(0 = not satisfied, 1 = satisfied, 2 = very satisfied) (8)	1 (1%)
4-point scale	
0, unsatisfied; 1, poor; 2, fair; 3, satisfied; 4, extremely satisfied (45,129)	2 (1%)
5-point scale:	
0 = not satisfied, 1 = slightly satisfied, 2 = moderately satisfied, 3 = satisfied, and 4 = very satisfied (26)	1 (1%)
Unsatisfied or subjectively worse (score: 1), no change (score: 2), mild improvement (score: 3), moderate improvement (score: 4), and significant improvement (score: 5) (5,57,87)	3 (2%)
6-point scale	1 (1%)
Ranging from "very good", "adequate", "none" (123)	
Visual Analogue Scale (VAS, 0-10)	**6 (4%)**
0 level: Not satisfied at all, a level of 10: completely satisfied (34,75,97,115,121,133)	6 (4%)
Questionnaires	
Comprehensive Satisfaction Questionnaire (PSQ-18). (93)	**2 (1%)**
6 Standardized telephone questions (e.g. 'How satisfied were you with laser treatment?,	1 (1%)
Would you recommend the treatment to others?) (51)	1 (1%)
Satisfaction reported without any scale reported (43,55,58,82,83,84,120)	**7 (5%)**
Percentile ranking by grade	
Percentage quartile grading	**3 (2%)**
Grade 1 = 0%–25%, minimal to no improvement/unsatisfied; Grade 2 = 26%–50%, moderate improvement/slightly satisfied; Grade 3 = 51%–75%, marked improvement/satisfied; and Grade 4 = >75%, near total improvement/very satisfied (1,125)	
Percentage quintile grading	
Satisfied (Grade 5), satisfied (Grade 4), not bad (Grade 3), unsatisfied (Grade 2), or very unsatisfied (Grade 1) (69)	2 (1%) 1 (1%)

Supplemental table 3. Outcome measurement instruments reported to measure domains

Scale used to measure domain of health-related quality of life	
Total reported	**4 (3%)**
Dermatology Life Quality Index (DLQI) (17)	1 (1%)
Skindex-16 (93)	1 (1%)
Burns Specific Health Scale (BSHS-B) (24)	1 (1%)
Quality of life reported without questionnaire reported (48)	1 (1%)

CHAPTER 4

A Generic Domain Set for a registry on laser treatments in dermatology: a Delphi process and consensus meeting

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What is already known?

- Lasers are used for many common and uncommon skin disorders.
- Due to the low prevalence of many of these skin disorders and the lack of uniform outcome measures, there is only low-quality evidence on the efficacy and safety of these laser treatments.
- The development of a Generic Outcome Set (GOS) to be used in daily practice for an international registry may improve harmonization of outcomes reported, standardized reporting and collection of relevant outcomes that are meaningful to patients.

What does this study add?

- A Generic Domain Set (GDS) as first part of the GOS, including the corresponding outcome subdomains, was developed for the future international Laser trEAtments in Dermatology (LEAD) registry, an international registry on laser treatments for various skin disorders.
- International consensus was reached on the 9 recommended outcome subdomains: appearance, affected surface area, texture of the surface, color, overall health-related Quality of Life, impact of disease/condition on physical activities of daily living, patient satisfaction (outcome/treatment), adverse events (>6 months), number of treatment sessions.
- This study shows that a GDS can be developed for a heterogeneous group of skin disorders and enables the next step in outcomes research, namely to reach consensus on the core outcome measurement instruments of the GOS.

What are the clinical implications of this work?

- The GDS and subsequently the core outcome measurement instruments will enable harmonization of outcomes reported, standardized reporting of treatment outcomes and collection of relevant outcomes that are meaningful to patients, thereby facilitating proper comparison of treatment results.
- Finally, the use of a GOS in the future LEAD registry may provide higher level evidence for effectiveness and safety of laser treatments for many uncommon skin disorders.

Summary

Background: There is insufficient evidence on the effectiveness and safety of laser treatments for many uncommon skin disorders. A registry that enables prospective and uniform use and proper reporting of relevant and meaningful outcomes may provide the much-needed evidence in this field.

Objective: This study aims to reach international consensus between key stakeholders on a generic outcome domain set (GDS). The GDS is defined as the minimum set of generic outcome domains, as part of the Generic Outcome Set (GOS) for use in the future International Laser TrEAtment Dermatology (LEAD) registry.

Methods: Twenty-six potentially relevant generic outcome subdomains were identified based on a literature review and input from the LEAD steering committee. These outcome subdomains were proposed to an international group of physicians and (parents of) patients with various skin disorders which could be treated with laser. We aimed to include experts and patients with scars, vascular lesions, pigmentary disorders, hair follicle related diseases, skin neoplasms and inflammatory disorders. During a 3-round Delphi process using online surveys, participants repeatedly rated the importance of the generic outcome subdomains on a nine-point Likert scale. Generic means that the subdomains should be applicable to all the included skin disorders. Participants could also propose other relevant subdomains. Consensus was pre-defined as at least 70% agreement on the importance of a generic subdomain among both stakeholder groups. The GDS was finalized during an online consensus meeting with representatives of each stakeholder group.

Results: A total of 96 physicians and 39 patients from 15 countries participated in the first Delphi round. During the two subsequent e-Delphi study rounds, 102 and 83 participants participated, respectively. After three rounds and a consensus meeting, consensus was reached on 9 generic outcome subdomains: appearance, affected surface area, texture of the surface, color, overall health-related Quality of Life, impact of disease/condition on physical activities of daily living, patient satisfaction (outcome/treatment), local adverse events (>6 months) and number of treatment sessions.

Conclusion: These generic outcome subdomains will enable standard reporting in the future LEAD registry. The next step will be to select outcome measurement instruments to score the generic outcome subdomains.

Introduction

During the last two decades, the continuous evolution of laser technology created therapeutic options for various skin disorders including cosmetic indications. These devices found application in treatments for scars, vascular lesions, pigmentary disorders, hair follicle related diseases, skin neoplasms and inflammatory disorders. (1) Many of these skin disorders meet the criteria of an orphan disease.

Due to their low prevalence, there is little scientific proof for efficacy or safety of laser treatments in these rare skin diseases. Additionally, heterogeneity of outcomes (i.e. domains) and measurement instruments has been demonstrated to hinder comparing treatment results and pooling of data between centers and countries. (2-5)

The current literature is insufficient to provide clinicians with guidance on appropriate indications and details of the optimal laser regimen. The development of an international registry for Laser trEAtments in Dermatology (LEAD) is therefore a critical step, enabling adequate international collaboration between clinicians and researchers in this field. Collecting relevant data of laser treatments of uncommon skin diseases will increase both the sample size and the reliability of conclusions.

Currently, there is no consensus on which outcomes should be reported in the future LEAD registry when evaluating outcomes of laser treatments in various uncommon skin disorders. A core outcome set (COS) facilitates harmonization of outcomes reported, standardized reporting of treatment outcomes and collection of relevant outcomes that are meaningful to patients in the future LEAD registry. A COS includes a minimum set of outcomes that should be measured and reported in clinical research or a registry when studying a specific health condition.(6) The COS development is already evident in various dermatological diseases, such as peripheral vascular malformations, atopic eczema, hidradenitis and congenital melanocytic naevi.(4) However, with so many uncommon skin diseases involved in the LEAD registry, reaching consensus on core domains, core subdomains and core outcome measurement instruments for each skin condition separate is virtually impossible. We, therefore, aim to develop one single generic core outcome set (GOS) that should be applicable to all the skin disorders treated with lasers. An agreed GOS involves *what* to measure (outcome domains and subdomains) and *how* to measure (outcome measurement instruments).(4)

The aim of this study is to develop a generic outcome domain set (GDS) for the future LEAD registry on laser treatments for various uncommon skin disorders.

Methods

This study was registered in the Core Outcome Measures for Effectiveness Trials (COMET) database (https://www.comet-initiative.org/Studies/Details/1134), the CS-COUSIN website (http://cs-cousin.org/LEAD) and the C3 website (https://www.c3outcomes.org). A detailed study protocol describing the Delphi process of the LEAD initiative and criteria for participant selection has been published previously.(7)

We followed the guidelines of the COMET initiative, the Cochrane Skin Group – Core Outcome Set Initiative (CS-COUSIN) and the HOME initiative. CS-COUSIN also provided methodological support. According to the HOME roadmap, outcomes (i.e concepts to be measured) were retrieved from a systematic review that has been published previously (8). In total, we identified 105 outcomes extracted from the 150 included studies. To avoid overlap and increase clarity, the potential outcomes were categorized into outcome domains according to the taxonomy of Dodd et al. (9) The categorization was discussed with patients (n=12), and with the LEAD steering committee (n=19). Later, the steering committee specified the outcome domains to more detailed outcome subdomains according to Lange et al. (10) This resulted in a list with 25 potential outcome subdomains that were presented during round 1 (see Table S1, Supporting Information).

Further definitions and descriptions of generic outcome domains and outcome subdomains can be found in Appendix S1, Supporting Information. We deviated from our previously published protocol, in which only outcome domains were foreseen.

Participants

Participants were recruited from the following international key stakeholder groups: (parents of) patients aged 18 or above with scars, vascular lesions, pigmentary disorders, hair follicle related diseases, skin neoplasms and inflammatory disorders treated with lasers and health professionals (experts and dermatologists) involved in laser dermatology. Moreover, we included representatives from relevant patient associations. (Parents of) Patients were invited to participate via the LEAD steering group, via national and international patient organizations and the social media channels of patient organizations. Laser experts and dermatologists were invited through personal networks of the LEAD steering committee. The invitations can be found in Appendix S2 and Appendix S3, Supporting Information.

Delphi survey

In an e-Delphi process we aimed to reach consensus on the GDS and the corresponding generic outcome subdomains. The Delphi process involved three online rounds for each stakeholder group. Participants received feedback on the consensus scores of the previous

round in both stakeholder groups. Individual participants could then decide to keep their original answers or to change their opinion in the next round, considering responses from the other participants.

Online surveys (LimeSurvey) were used to evaluate the importance of the potential generic outcome subdomains. The potential generic outcome subdomains (25 subdomains) formed the content for the online surveys in English.

Before the first round the survey was checked for clarity and comprehensibility by two members of the LEAD steering committee and one American patient.

On the first page of each survey, the details of the study and key objectives were presented. Particularly, the setting of a registry for laser treatments of various uncommon skin disorders was stressed. To illustrate the diversity of skin disorders involved, we included clinical images of various skin disorders.

A total of 3–4 weeks was anticipated in the protocol to complete each survey per study round. In each e-Delphi survey, the importance of generic outcome subdomains was rated using the Grading of Recommendations Assessment, Development and Evaluations approach. The scale ranged from 1 to 9 and was categorised as follows: 1–3 'not important'; 4–6 'important but not critical'; and 7–9 'critical'. In the first survey rounds participants had the option to propose new generic outcome subdomains.

During the first round, we collected baseline characteristics of the participants. Before being introduced in the second Delphi round, the newly suggested generic outcome subdomains were checked by the LEAD steering committee to determine whether they could measure treatment effect and whether they were truly new generic outcome subdomains. In the second and third Delphi round, participants received feedback on the scores of the previous study round from each stakeholder group. Then we asked participants to repeat their rating for the generic outcome subdomains on which consensus had not been reached. Participants who completed the first Delphi round were invited for the second and the third Delphi round.

Definition of concensus

The definition of consensus for the Delphi was based on the protocol previously reported. (7) Consensus that a generic outcome subdomain item should be included in the GDS 'Consensus in' is defined as approval of the generic outcome subdomain by the vast majority (70 %) of all stakeholder groups that score 7, 8 or 9 with fewer than the minority (15 %) of panellists scoring 1–3. On the contrary, 'consensus out' is defined as 70% or more of all stakeholder groups scoring as 1 to 3 and less than 15% scoring as 7 to 9.

After round 3, we used the following definitions for feasibility reasons (deviation from the protocol): generic outcome subdomains that had not met the threshold for 'consensus in' and were rated 'important' by less than 50% in all stakeholder groups were categorized as 'no consensus, voting if needed' and assumed to be excluded from

the GDS if there were no strong voices or comments during the meeting to re-vote . The generic outcome subdomains that had not met the threshold for 'consensus in' but were rated 'important' by at least 50% in at least one stakeholder group were categorized as 'no consensus, voting required'. This resulted in the classification of each generic outcome subdomain as 'consensus in', 'no consensus, voting if needed' or 'no consensus, voting required' after round 3.

Consensus meeting

The last step of the Delphi study consisted of an online consensus meeting (Zoom Video Communications, Inc., V.5.0.1) with healthcare professionals and patients to agree on the generic outcome subdomains for the LEAD registry. Participants who completed at least two Delphi rounds were invited to join the meeting. The online meeting was chaired by a LEAD steering committee member (A.W.), with experience in the laser field and international Delphi exercises. The moderators (A.W. and F.F) presented the response rates of Delphi round 3 according to the three above-mentioned categories of classification. The generic outcome subdomains in the categories 'consensus in' and 'no consensus, voting if needed' were not voted on, unless there were strong voices or comments during the meeting to re-vote. For the category 'no consensus, voting required', discussion and voting took place via an online poll on the video-conferencing platform. Whenever more than 70% of the participants in both stakeholder groups voted 'in', the generic outcome subdomain was included in the GDS.

Statistical analyses

We used Microsoft Excel for data analyses. The percentage agreement in the e-Delphi rounds were calculated for all generic outcome subdomains and rounded to the nearest whole percentage.

Ethical requirements

The Medical Ethics Review Committee of the Academic Medical Centre in Amsterdam (reference number W19_290 # 18·336) confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study. Participants gave online consent at the first survey round for their data to be used anonymously.

Results

Participant characteristics

In total, 135 participants from 15 countries participated in the first Delphi round. Of these, 96 were physicians from 15 countries. A total of 39 patients with various skin diseases treated with laser were enrolled in the first round. This included patients

with scars, vascular lesions, pigmentary disorders, hair follicle related diseases, skin neoplasms and inflammatory disorders. The characteristics of participants in round 1 are presented in Table 1.

Table 1. Characteristics of the participants in e-Delphi round 1.

Characteristics Physicians	**N (%)**	**Characteristics Patient/Parents**	**N (%)**
Total group	96 (100)	Total group	39 (100)
Specialty		Country of residence	
Laser Dermatology	55 (57.3)	United States	7 (18.0)
Dermatology	57 (59.4)	Canada	2 (5.13)
Plastic surgery	3 (3.1)	Europe	23 (1.4)
Other	3 (3.1)	Africa-Middle East	7 (7.5)
Years of experience			
		Type of disease treated (if indicated)	
0-<5 years	21 (9.0)	Vascular	9 (23.1)
5-<10 years	16 (21.0)	Pigmented	6 (15.4)
10-<15 years	17 (18.0)	Inflammatory	7 (17.9)
15-<20 years	19 (25.7)	Benign Tumours	8 (20.5)
>20 years	23 (26.3)	Hair follicle-related	4 (10.3)
Continent of employment			
Unites States	9 (24.6)		
Canada	3 (3.1)		
Europe	44 (9.0)		
Africa- Middle East	36 (5.4)		
Asia	4 (5.4)		
Type of hospital			
University hospital	68 (83.2)		
Urban hospital	10 (14.4)		
Private clinic	40 (8.4)		
Number of new patients treated annually			
0–20	6 (9.0)		
20–100	9 (45.5)		
100–200	6 (21.6)		
200–400	16 (16.8)		
>400	57 (7.2)		

During the two subsequent e-Delphi study rounds, 102 and 83 persons participated, respectively. Table 2 shows the number of participants including the response rates (RR) per e-Delphi round. During the first round we could not measure the RR as the experts and patients were invited via different ways: national and international patient organizations and their social media channels. Overall, the RR was 70% or more in the second and third e-Delphi round.

Table 2. Votes during the e-Delphi rounds

Domain	Generic Outcome Subdomain	Round 1		Round 2		Round 3		Delphi
		Phys (N=96) **	Pat (N=39)	Phys (N=71) RR= 73%	Pat (N=31) RR: 79%	Phys (N=56) RR=78%	Pat (N=24) RR=77%	Consensus round 1 Consensus round 2 Consensus round 3
Signs as assessed by physician	Appearance of the skin disease	92.5	83.0	-	-	-	-	•
	Texture of the surface	80.0	67.0	72.0	70.0	-	-	•
	Color	82.0	71.0	-	-	-	-	•
	Number of lesions	63.7	56.0	60.0	58.0	57.0	62.0	n/a
	Thickness of the lesion*	n/a	n/a	63.0	65.0	64.0	65.0	n/a
	Affected surface of the area (size)	61.2	61.0	66.0	66.0	67.0	71.0	n/a
Signs as assessed by patient	Appearance of the skin disease	80.0	72.0	-	-	-	-	•
	Texture of the surface	52.5	63.0	71.0	68.0	65.0	67.0	n/a
	Color	66.0	60.0	72.0	65.0	67.0	73.0	n/a
	Number of lesions	61.0	43.0	61.0	61.0	59.0	68.0	n/a
	Thickness of the lesion*	n/a	n/a	65.0	62.0	67.0	60.0	n/a
	Surface of the affected area (size)	51.2	50.0	59.0	72.0	59.0	74.0	n/a
	Disease specific symptoms	46.2	58.0	67.0	70.0	63.0	68.0	n/a
Quality of Life	Overall health-related Quality of Life	77.5	73.0	-	-	-	-	•
	Impact of disease/condition on social functioning	67.0	68.0	72.0	73.0	-	-	•
	Impact of disease/condition on physical activities of daily living	66.0	45.0	69.0	76.0	72.0	81.0	•

Table 2. Continued.

Domain	Generic Outcome Subdomain	Round 1		Round 2		Round 3		Delphi
		Phys (N=96) **	**Pat (N=39)**	**Phys (N=71)** RR= 73%	**Pat (N=31)** RR: 79%	**Phys (N=56)** RR=78%	**Pat (N=24)** RR=77%	Consensus round 1 Consensus round 2 **Consensus round 3**
Satisfaction	Patient satisfaction with outcome	88.0	78.0	-	-	-	-	•
	Patient satisfaction with treatment	53.0	68.0	70.0	73.0	-	-	•
Adverse events	Systemic adverse events (temporary)	50.0	38.0	54.0	56.0	52.0	63.0	n/a
	Local adverse events (temporary)	85.0	53.0	65.0	60.0	59.0	63.0	n/a
	Systemic adverse events (permanent)*	n/a	n/a	59.0	72.0	57.0	76.0	n/a
	Local adverse events (permanent)*	n/a	n/a	71.0	72.0	-	-	•
Proposed by participants*	Number of sessions*	n/a	n/a	66.0	67.0	73.0	68.0	n/a
	Dermatoscopy*	n/a	n/a	51.0	62.0	53.0	59.0	n/a
	Tolerability of products*	n/a	n/a	50.0	56.0	47.0	62.0	n/a

* Proposed by participants

**The Response rate of the first round could not be determined, as patients and experts were invited via various ways, via members of the steering committee,via social media accounts and patient organizations

Delphi rounds

Table 2 provides an overview of the results of the Delphi procedure of each stakeholder group. Of the list with comments and suggested generic outcome subdomains during the first round, 7 generic outcome subdomains were eventually added to the second e-Delphi round. (see Table 2 'proposed by participants'). After the third e-Delphi round, consensus was reached for 9 generic outcome subdomains: appearance, affected surface area, texture of the surface, color, overall health-related Quality of Life, impact of disease/condition on physical activities of daily living, patient satisfaction (outcome/treatment), adverse events (>6 months), number of treatments. Eventually, none of the generic outcome subdomains reached consensus on 'non-importance'.

Consensus meeting

During the final online consensus meeting, a maximum of 32 participants from 10 countries participated, including 11 patients, 5 patient representatives and 16 experts. Table 3 presents the results of the votes and comments raised during the meeting.

During the consensus meeting we reviewed all (included and ' no consensus, voting required')generic outcome subdomains, of which, 'patient satisfaction' was discussed more extensively. Due to overlap it was suggested to combine both '*patient satisfaction with the outcome*' and '*patient satisfaction with treatment'* into 1 subdomain. A re-vote was held and both subdomains were kept separately in the GDS. According to the taxonomy of Lange et al. 'Satisfaction with treatment' is considered as the first level subdomain below the top-level domain 'satisfaction'. '(See for definitions Appendix S1)

Of the 'no consensus, voting required' generic outcome subdomains (n=6), consensus was reached on including '*affected surface area (size) assessed by the physician' and 'number of sessions'* in the GDS. The 'no consensus, no consensus, voting if needed' were discussed but not voted on, as there were no strong voices or comments during the meeting to re-vote.

Another essential comment was raised during the meeting on the concept of 'permanent' adverse events, both local and systemic, and the subsequent lack of clarity about this generic outcome subdomain. Based on this discussion, an additional revote was held on the concept of 'permanent local adverse events' by means of permanent defined as >6 months. The concept of 'local adverse events >6 months' was approved to be in the GDS.

Table 3. Results of online consensus meeting

Generic Outcome domains	Generic Outcome Sub domains	Results after last e-Delphi round	Votes	Comments from consensus meeting
Signs as assessed by physician	Appearance	+	n/a	
	Texture of the surface	+	n/a	
	Color	+	n/a	
	Number of lesions	-		
	Thickness of the lesion	-		
	Size	-	~	
	Surface of the affected area (size)	?	~	Outcome: change over time. Could measure the surface area before, after or the change during treatment.
Symptoms/ signs as assessed by patient	Appearance	+	n/a	May also cover texture, color.
	Texture	-	~	
	Color	?	~	
	Number of lesions	-	~	
	Affected surface of the area (size)	?	Vote to include (76%)	
	Disease specific symptoms	-	~	
quality of life	Overall health-related quality of life	+	n/a	
	Social functioning	+	n/a	
	Physical functioning	+	n/a	

Table 3. Continued.

Generic Outcome domains	Generic Outcome Sub domains	Results after last e-Delphi round	Votes	Comments from consensus meeting
Delivery of Care	Patient satisfaction with outcome	+	n/a	Could be associated with generic outcome subdomain level 2.
	Patient satisfaction with treatment	+	Vote to include as separate generic outcome subdomain (85%)	In future there might be 1 instrument in the Generic outcome Measurement Set that covers both generic outcomes.
Adverse Events	Systemic adverse events (temporary)	-	~	
	Local adverse events (temporary)	-	~	
	Systemic adverse events (permanent)	?	Vote to include (82%)	Remark: 'permanent' is in the meeting discussed to be more concrete and defined as > 6 months
	Local adverse events (permanent)	+	n/a	Remark: 'permanent' is in the meeting discussed to be more concrete and defined as > 6 months
Proposed by participants	Tolerability of topical products	-	~	
	Dermatoscopy	-	~	
	Number of treatmens (sessions)	?	Vote to include (87%)	

Final GDS

After three Delphi rounds and a consensus meeting, the GDS on domain level included six generic outcome domains containing nine subdomains. (Table 4)

Table 4. Final GDS for the LEAD registry

Core area	Generic Outcome Domain	Generic outcome Subdomain **first level**	Generic outcome Subdomain **second level**
Physical/ clinical	*Signs as assessed by physician*	1.Appearance of the skin disease	2.Texture of the surface 3. Color 4. Affected surface area (size)
	Signs as assesesd by patient	Appearance of the skin disease	
Life impact	*Quality of Life*	5.Overall QoL	6. Impact of disease/condition on physical activities of daily living
	Satisfaction	7*.Patient satisfaction with treatment	7.* Patient satisfaction with outcome
	Adverse Events	8.Local adverse events (>6 months)	
	Delivery of care	9.Number of sessions	

Patient satisfaction with treatment and patient satisfaction with outcome is taken together as 1 generic outcome subdomain.

Discussion

With this international consensus-based study, involving (parents/representatives of) patients and health care professionals as key stakeholders, we identified the generic outcome domains and subdomains for the future Laser trEAtments in Dermatology (LEAD) registry. Eventually, 5 generic outcome domains comprising 9 generic outcome subdomains were included in the GDS.

The methods used in this consensus study are in accordance with internationally agreed standards for COS development, i.e. the guidelines of the COMET initiative and CS-COUSIN.(10) Compared to other previously conducted dermatological COS that were focused on one specific disease, our project is exceptional, as it will provide a minimum set of outcomes applicable for a heterogeneous group of skin disorders.

A potential disadvantage is that unique aspects related to a specific skin disease may not be captured in a GOS. Consequently, interpretation of measurements of generic outcome subdomains could fail to reflect true treatment-related improvement. However, with so many uncommon skin diseases treated with lasers, it is not feasible to develop a COS (outcome (sub)domains, measurement instruments and contextual factors) for

each skin disorder apart. In addition, strong support for the concept of generic outcomes is evident from the overlap of currently available COSs. Moreover, our GDS is largely comparable to the CDS of a range of heterogeneous skin conditions such as hidradenitis, vascular malformations, atopic eczema, acne and vitiligo.(11-16). Finally, our GDS is the minimum set of (sub)domains to be documented, while physicians may always add condition-specific measures when necessary. The taxonomy of Lange et al. could help to include further levels of sub-domains.

A known limitation in COS studies is the problem of possibly having a different group of international participants in the Delphi study in comparison to the final consensus meeting, which might affect the final GDS. During our consensus meeting, an equal number of participating (representatives of) patients (n=16) and experts (n=16) were present. The discussions during the meeting were both patient and expert-led which is similar to that of other COS development projects.(11-14)

The use of an online consensus meeting, especially during the COVID-19 pandemic, allowed us to meet with patients and laser experts from all over the world. Yet, international time differences might have been a barrier to join for all invited participants. Moreover, it may be that participants were less involved than in a face-to-face meeting. Still, we believe online consensus meetings are an effective way to discuss and directly vote on the generic outcome subdomains with the support of a predefined meeting framework.

To the best of our knowledge, this study represents the first attempt to provide one GDS for a heterogeneous group of skin disorders. We recommend to use the GDS as a minimum reporting standard in the international the future Laser trEAtments in Dermatology (LEAD) registry. Future research is needed to further define how and when to measure these generic outcome domains.

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References

1. Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology: four decades of progress. J Am Acad Dermatol. 2003;49(1):1-31; quiz -4.
2. Kearney M, Treadwell J, Marshall M. Overtreatment and undertreatment: time to challenge our thinking. Br J Gen Pract. 2017;67(663):442-3.
3. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13:132.
4. Prinsen CAC, Spuls PI, Kottner J, Thomas KS, Apfelbacher C, Chalmers JR, et al. Navigating the landscape of core outcome set development in dermatology. J Am Acad Dermatol. 2019;81(1):297-305.
5. Prinsen CAC, Mokkink LB, Bouter LM, Alonso J, Patrick DL, de Vet HCW, et al. COSMIN guideline for systematic reviews of patient-reported outcome measures. Qual Life Res. 2018;27(5):1147-57.
6. Kirkham JJ, Gorst S, Altman DG, Blazeby J, Clarke M, Devane D, et al. COS-STAR: a reporting guideline for studies developing core outcome sets (protocol). Trials. 2015;16:373.
7. Fransen F, Spuls P, Alam M, Badawi A, Boixeda P, Haedersdal M, et al. Generic outcome set for the international registry on Laser trEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on what to measure. BMJ Open. 2020;10(6):e038145.
8. Fransen F, Tio D, Prinsen CAC, Haedersdal M, Hedelund L, Laubach HJ, et al. A systematic review of outcome reporting in laser treatments for dermatological diseases. J Eur Acad Dermatol Venereol. 2020;34(1):47-53.
9. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J Clin Epidemiol. 2018;96:84-92.
10. Lange et al. Lange T, Kottner J, Weberschock T et al. Outcome assessment in dermatology clinical trials and Cochrane reviews: call for a dermatology-specific outcome taxonomy. J Eur Acad Dermatol Venereol 2021; 35:523–35
11. Horbach SER, van der Horst C, Blei F, van der Vleuten CJM, Frieden IJ, Richter GT, et al. Development of an international core outcome set for peripheral vascular malformations: the OVAMA project. Br J Dermatol. 2018;178(2):473-81.
12. Kottner J, Jacobi L, Hahnel E, Alam M, Balzer K, Beeckman D, et al. Core outcome sets in dermatology: report from the second meeting of the International Cochrane Skin Group Core Outcome Set Initiative. Br J Dermatol. 2018;178(4):e279-e85.
13. Thorlacius L, Ingram JR, Garg A, Villumsen B, Esmann S, Kirby JS, et al. Protocol for the development of a core domain set for hidradenitis suppurativa trial outcomes. BMJ Open. 2017;7(2):e014733.
14. Eleftheriadou V, Thomas K, van Geel N, Hamzavi I, Lim H, Suzuki T, et al. Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. Pigment Cell Melanoma Res. 2015;28(3):363-9.
15. Thiboutot DM, Layton AM, Chren MM, Eady EA, Tan J. Assessing effectiveness in acne clinical trials: steps towards a core outcome measure set. Br J Dermatol. 2019;181(4):700-6.
16. Gerbens LAA, Apfelbacher CJ, Irvine AD, Barbarot S, de Booij RJ, Boyce AE, et al. TREatment of ATopic eczema (TREAT) Registry Taskforce: an international Delphi exercise to identify a core set of domains and domain items for national atopic eczema photo- and systemic therapy registries. Br J Dermatol. 2019;180(4):790-801.

Supporting Information

Appendix S1: list of definitions of outcomes
Appendix S2: invitation Delphi rounds for patients
Appendix S3: invitations Delphi rounds for physicians

Appendix S1: list of definitions of outcomes

Core area	An umbrella term for a group of associated outcome domains. An aspect of health of a health condition that needs to be measured to appropriately asses the effect of a health intervention. Core Areas are broad concept consisting of a number of more specific concepts named outcome domains. Example: "life impact"
Outcome domain	Component of a Core Area: a concept to be measured, a further specification of an aspect of health, categorized within a Core Area. Example: Quality of Life
Outcome Subdomain level 1	Component of an Outcome Domain: a concept to be measured, a further specification of an aspect of health, categorized within an Outcome Domain. Example: Satisfaction with treatment
Outcome Subdomain level 2	Component of an Outcome Domain a concept to be measured, a further specification of an aspect of health, categorized within an Outcome Subdomain. Example: Satisfaction with outcome

Outcome definitions retrieved from Lange et al. (2020) (10)

LEAD

International Laser TrEAtment Dermatology Registry

Dear sir/madam,

On behalf of the steering committee, we are pleased to invite you to participate in an international eDelphi exercise to develop the generic outcomes for the LEAD registry. LEAD stands for International Laser TrEATment Dermatology and focuses on patients treated for **any medical skin condition with any type of laser**. This upcoming multi-center observational registry facilitates the evaluation of the clinical effectiveness and safety of laser treatments in clinical practice.

eDelphi exercise
We believe that your experience will benefit the eDelphi survey. The Delphi will anonymously survey experts and patients on what outcomes should be included in the LEAD registry database, if necessary with three rounds. Patients and professionals will have an equal say in the study, so your input is extremely important.

What is expected
We will ask you to rate the importance (not important, important or **essential**) of the proposed selection of outcomes to be captured in the registry. These outcomes constitute an agreement as to **what (essential)** should be measured in the LEAD registry, for various medical skin conditions and laser treatments. In round 2 and 3, information will be provided on the results of the previous round to encourage agreement.

Please use the following link to register your interest in taking part in the 1st round:

The eDelphi registration will remain open until April 1 2020. Participants will be acknowledged in the publication of the results if they completed all three rounds.

We would be grateful if you could also forward this letter to members of your organizations (patients, caregivers of patients or patient representatives) with a particular interest or experience in laser treatments, who you think would be willing to participate in this initiative. You can read more about the study in the attached information sheet. Please feel free to contact if you have any comments or questions.

We look forward to working with you on this exciting initiative.

Yours sincerely,

On behalf of the LEAD registry steering committee,

Albert Wolkerstorfer Frederike Fransen Phyllis Spuls

Completion of the entire eDelphi process
It is very important that you complete the questionnaires in each round, even if the eDelphi group does not share the same opinions as you. The reliability of the results is likely to be compromised if participants drop out of the study before it is complete. If participants drop out because they feel their opinions are in the minority, the final results will overestimate the degree of agreement on the outcomes.

LEAD

International Laser TrEAtment Dermatology Registry

Dear colleague,

On behalf of the steering committee, we are pleased to invite you to participate in an international eDelphi exercise to develop the generic outcomes for the LEAD registry. LEAD stands for International Laser TrEATment Dermatology. This upcoming multi-center observational registry facilitates the evaluation of the clinical effectiveness and safety of treatments in clinical practice.

eDelphi exercise
We believe that your experience in laser research and treatments will benefit the eDelphi survey. The Delphi will anonymously survey experts and patients on what outcomes should be included in the LEAD registry database, if necessary with three rounds that are followed by a consensus meeting to discuss remaining areas of disagreement.

What is expected
We will ask you to rate the importance (not important, important or **essential**) of the proposed selection of outcomes to be captured in the registry. These outcome domains and outcomes constitute an agreement as to **what (essential)** should be measured in the LEAD registry, for various medical skin conditions and laser treatments. In round 2 and 3, information will be provided on the results of the previous round to encourage agreement.

Please use the following link to register your interest in taking part in the 1st round:

The eDelphi registration will remain open until April 1 2020. Participants will be acknowledged in the publication of the results if they completed all three rounds.

We would be grateful if you could also forward this letter to members of your organizations (clinicians, patients, caregivers of patients or patient representatives) with a particular interest or experience in laser treatments, who you think would be willing to participate in this initiative.

We look forward to working with you on this exciting initiative.

If you have questions or concerns, please contact us at leadregistry@gmail.com.
Yours sincerely,

On behalf of the LEAD registry steering committee,

Albert Wolkerstorfer Frederike Fransen Phyllis Spuls

Completion of the entire eDelphi process
It is very important that you complete the questionnaires in each round, even if the eDelphi group does not share the same opinions as you. The reliability of the results is likely to be compromised if participants drop out of the study before it is complete. If participants drop out because they feel their opinions are in the minority, the final results will overestimate the degree of agreement on the outcomes.

PART II

Laser Treatments and Safety in Clinical Practice

CHAPTER 5

Laser treatment of epidermal nevi: a multicenter retrospective study with long-term follow-up

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Abstract

Background: Patients with epidermal nevi strongly demand cosmetic improvement. Laser treatment appears appealing and is frequently used in clinical practice. Nevertheless, large series with long-term follow-up are missing preventing to draw definitive conclusion on its real benefit.

Objective: To evaluate long-term effectiveness and safety of lasers for epidermal nevi.

Methods: Bicentric retrospective cohort study including all patients treated with a laser for an epidermal nevus with more than one year follow-up.

Results: Seventy patients were treated for different types of epidermal nevi, mostly with ablative lasers: 23 verrucous epidermal nevi, 16 nevi sebaceous, 26 Becker nevi, 2 inflammatory linear verrucous epidermal nevi, 1 smooth muscle hamartoma, 1 rounded and velvety epidermal nevus, and 1 nevus lipomatosus superficialis. The follow-up period ranged between 12 and 127 months (median 37 months). Better results, less recurrences, and higher patients' satisfaction were noted in verrucous epidermal nevi than in nevi sebaceous. Q-switched lasers failed to show any degree of improvement in almost all patients with Becker nevus.

Limitations: The retrospective nature of the study.

Conclusions: Ablative lasers can treat verrucous epidermal nevi with good long-term aesthetic results, but they have limited long term efficacy for nevus sebaceous. Q-switched lasers failed to improve Becker nevi.

Capsule summary

- In the absence of satisfactory treatments for epidermal nevi, lasers are promising.
- Our study demonstrates that improvement with ablative lasers varies between verrucous and sebaceous nevi, with better long-term results in verrucous nevi. It also shows that Becker nevus is not a good indication for Q-switched lasers.

Introduction

Epidermal nevi (EN) are a heterogeneous group of hamartomatous skin lesions defined by the proliferation of keratinocytic, glandular, follicular, or muscular components of the epidermis. Multiple components are usually present in a single lesion but the type is defined according to the predominant cell types. The most common types are the verrucous epidermal nevus (VEN), also called keratinocytic epidermal nevus, and the nevus sebaceous (NS). Other types include inflammatory linear verrucous epidermal nevus (ILVEN), Becker nevus (BN), smooth muscle hamartoma (SMH), nevus comedonicus, porokeratotic eccrine nevus [1], rounded and velvety epidermal nevus (RAVEN), [2] and nevus lipomatosus superficialis (NLS).[3]

EN has an incidence of 1-3 cases /1000 births [4] and represents a frequent motive for consultation in dermatology, with an aesthetic complaint and a strong cosmetic demand for removal. Since the surgical excision is often limited by the size and the location of EN, many non-surgical techniques have been proposed, including cryotherapy, electrocautery, dermabrasion, and chemical peels.[5] Unfortunately, such approaches give inconsistent results and have a strong risk of scars. Lasers have been also proposed for treating different types of EN with encouraging results. Nevertheless, most articles are case reports or series with small numbers of participants and generally a limited follow-up, thus preventing reliable conclusions on the true benefit of laser therapy for EN. [6-50]

The objective of this study was to assess the long-term effectiveness and safety of laser approaches in treating the different types of EN.

Methodology

We conducted a retrospective cohort study in the dermatology departments of the University Hospital of Nice in France and the Academic Medical Center of the University of Amsterdam in The Netherlands.

We included all patients with any type of EN who were treated with a laser in our departments between 2007 and 2018. All the patients were contacted by telephone to assess their auto-evaluation and satisfaction, and asked to send a clear picture to assess the long-term effectiveness of the laser treatment. We excluded all patients with a follow-up of less than one year, patients who could not be contacted, and patients treated only for hair removal of BN. All patients with an immediate complete failure of the laser treatment were included as no follow-up was needed.

The laser treatment was performed by three dermatologists experienced in lasers (FLD, AW, TP). Digital color photographs were taken at baseline, soon after the last session, and at the last follow-up. All photographs were then evaluated by two independent dermatologists (AA, FF) for physician global assessment after the treatment (short-term PGA) and at the last follow-up (long-term PGA). ST-PGA and LT-PGA were graded from 0 to 6 (0= 100% improvement, 1= 90-99% improvement, 2= 50-89%, 3= 25-49%, 4= 1-24%, 5= no improvement, 6= worsening). Patients were asked for their satisfaction (not satisfied, satisfied, very satisfied) and self-evaluation from 0-5 (0= cleared, 1= almost cleared, 2= good improvement, 3= slight improvement, 4= no change, 5= worse) at the last follow-up. Any degree of recurrence or persistent side-effects, including scarring, seen by the dermatologist or mentioned by the patient was noted. Age, gender, lesion characteristics, and site were noted, and results were analyzed for each type of EN.

Results

A total of 88 patients with EN were treated in both centres with various lasers between October 2007 and august 2018. Eight patients were lost to follow-up and unreachable (4 VEN, 2 NS, 2 BN), and ten patients were treated recently with a follow-up of less than one year (6 VEN, 1 NS, 2 BN, 1 RAVEN). A total of 70 patients were included. 23 of them had VEN, 16 had NS, 26 had BN, 2 had ILVEN, and the remaining three had RAVEN, NLS, and SMH. The follow-up period ranged between 12 and 127 months with a mean of 47.3 months and a median of 37 months. Age, laser type, improvement, scarring, recurrence, and the follow-up period of each patient are shown in the tables 1-4.

Table 1. Characteristics and results of verrucous epidermal nevus patients treated with laser

Patients		Lesion		Treatment		Results						Follow-up
N	Age, gender	Site	Size	Type (and number of sessions)	Parameters	PGA-ST	PGA-LT	Patients' self evaluation	Patients satisfaction	Recurrence	Scar	
Verrucous Epidermal Nevus												
1	14y,M	Nose	Small	Er: YAG (1)	3 mm, 13 J / cm2	1	1	1	S	No	No	1y
2	15y,F	Neck	Small	Er: YAG (1) then CO2 (2)	3 mm, 13 J/ cm2 N/A	1	1	1	S	No	Partial	4y 6m
3	23y,M	Neck	Medium	Er YAG (1)	2.5 mm, 13 J / cm2	1	2	2	S	Partial	No	4y 3m
4	17y,F	Sternal	Small	Er YAG (2)	2.5 mm, 13 J / cm2	3	Absent	2	S	Partial	No	6y 2m
5	30y,F	Hand	Medium	CO2 (2)	150-200 mJ / cm2	4	6	5	NS	Complete	Yes	4y 8m
6	51y,M	Scalp	Medium	Er YAG (1)	2.5 mm, 13 J / cm2	0	2	1	VS	Partial	No	1y 11m
7	16y,F	Eyelid	Small	Er YAG (2)	1.5 mm, 10 J / cm2	1	1	1	S	No	No	2y 6m
8	16y,M	Neck	Small	Er YAG (1)	3.5 mm, 10 J / cm2	Absent	2	4	NS	Partial	No	8y 10m
9	41y,F	Palmar	Medium	Er YAG (2)	3.5 mm, 16 J / cm2	2	5	3	S	Complete	No	2y 10m
10	14y,F	Lower lip	Small	QS 532 (1)	2 mm, 4 J / cm2	3	3	2	S	No	No	5y 9m
11	17y,F	Forearm	Medium	Er YAG (1)	1.5-3 mm, 10 J / cm2	1	1	1	VS	No	Hypo pigmentation	1y 8m

Table 1. Continued.

Patients		Lesion		Treatment		Results						Follow-up
N	Age, gender	Site	Size	Type (and number of sessions)	Parameters	PGA-ST	PGA-LT	Patients' self evaluation	Patients satisfaction	Recurrence	Scar	
12	18y,F	Neck	Small	Er YAG (2)	2.5 mm, 13 J / cm2	2	3	3	NS	No	Yes	6y 4m
13	6y,F	Hemicorporal	Large	Er YAG (2) armpit only	2.5 mm, 13 J / cm2	1	2	1	S	Partial	No	3y 1m
14	16y,M	Scapular	Medium	Er YAG (1)	3 mm, 16 J / cm2	2	4	2	S	No	Yes	1y 9m
15	18y,F	Scalp	Medium	CO2 (1), Er YAG (2)	2 mm, 225 mJ/cm2 2.5 mm, 10 J / cm2	1	1	1	S	No	Yes	1y 3m
16	13y,M	Armpit	Large	CO2 (1)	5-7 W	0	2	1	VS	Superficial	No	1y 6m
17	5y,M	Neck	Small	Er YAG (1)	10-13 J / cm2	2	5	4	NS	Complete	No	4y 9m
18	9y,M	Neck	Small	CO2 (1)	5W then 2.5 W	1	1	1	VS	No	No	1y 10m
19	12y,M	Axilla,groin	Small	CO2 (2)	2 mm, 15-25 W - 225 mJ	2	2	2	S	No	No	1y
20	49y,F	Shoulder, elbow	Medium	QS 755 (3)	2-3 mm, 10-16 J / cm2	4	2	1	S	Partial	No	7y
21	24y,F	Abdomen	Small	CO2 (2)	N/A	2	0	0	S	No	No	5y
22	12y,F	Thorax	Small	Fr CO2 (2)	N/A	2	0	0	S	Complete	No	7y
23	11y,F	Forehead	Small	CO2 (1)	2 mm, 200 mJ, 17 W	2	1	1	S	No	Yes	2y

PGA-ST= Short Term-Physician Global Assessment; PGA-LT= Long Term-Physician Global Assessment; VS= Very Satisfied; S= Satisfied; NS= Not Satisfied

Table 2. Characteristics and results of nevus sebaceous patients treated with laser

Patients		Lesion		Treatment		Results						Follow-up
N	Age, gender	Site	Size	Type and sessions	Parameters	PGA-ST	PGA-LT	Patients' self evaluation	Patients satisfaction	Recurrence	Scar	
Nevus sebaceous												
24	13y,M	Forehead	Small	Er YAG (1)	2.5 mm, 16 J / cm2	3	3	2	VS	Partial	Minimal	2y 3m
25	10y,M	Cheek	Small	Pulsed CO2 (1)	150 mJ, 10 Hz	5	Absent	4	NS	Complete	No	5y 4m
26	10y,F	Retro auricular	Small	Er YAG (2)	2.5 mm, 10 J / cm2	1	Absent	3	NS	Complete	Yes	10y 7m
27	18y,F	Cheek	Small	Er YAG (2)	2.5 mm, 10 J / cm2	3	2	2	S	No	Yes	7y 5m
28	7y,F	Cheek	Small	Er YAG (2)	2.5 mm, 10 J / cm2	4	5	3	S	Complete	No	5y 6m
29	13y,M	Cheek	Small	CO2 and Fr CO2 (1)	8 mJ and 150 mJ/cm2	2	2	2	S	Partial	Yes	4y 6m
30	7y,F	Forehead	Small	Test Er YAG (1)	13 J / cm2	4	5	4	NS	Complete	No	4y 9m
31	17y,M	Neck	Small	SP CO2 (1)	8 W then 3 W	1	2	1	VS	Partial	No	3y 6m
32	16y,M	Cheek	Small	SP CO2 (1)	5 W	6	5	4	NS	Complete	No	1y 7m
33	16,F	Nasal ala	Small	Er YAG (2)	3.5 mm, 16 J / cm2	3	Excised	4	NS	Complete	No	1y 1m
34	16y,M	Neck	Small	CO2 (1)	2mm, 7-10W, 225mJ	2	6	5	NS	Partial	Keloid	2y

Table 2. Continued.

Patients		Lesion		Treatment		Results						Follow-up
N	Age, gender	Site	Size	Type and sessions	Parameters	PGA-ST	PGA-LT	Patients' self evaluation	Patients satisfaction	Recurrence	Scar	
35	29y,F	Cheek	Small	CO2 (1)	2mm, 20 then 3.5W	2	1	1	S	Partial	No	3y
36	20y,M	Chin	Small	CO2 (1)	N/A	3	6	5	NS	complete	Yes	1y 6m
37	14y,M	Neck	Small	CO2 (1)	1mm, 3W, 225mJ	2	1	1	S	Partial	No	2y
38	16y,F	Earlobe	Small	CO2 (1)	2mm, 15 then 6 W	2	1	1	S	Partial	No	3y
39	16y,M	Forehead	Small	CO2 (1)	7 W, 225 mJ	2	0	0	VS	No	No	2y

PGA-ST= Short Term-Physician Global Assessment; PGA-LT= Long Term-Physician Global Assessment; VS= Very Satisfied; S= Satisfied; NS= Not Satisfied

Table 3. Characteristics and results of Becker nevus patients treated with laser

Patients		Lesion		Treatment	Results						Follow-up
N	Age, gender	Site	Size	Type (and number of sessions)	PGA-ST	PGA-LT	Patients' self evaluation	Patients satisfaction	Recurrence	Scar	
Becker Nevus											
40	16y,M	Flank	Large	Test QS 755 and QS 532	5 both	5	4	NS	No improvement	No	1y 3m
41	22y,F	Cheek	Small	Test QS 755 and QS 532	5 both	-	4	NS	No improvement	No	4y 5m
42	15y,F	Shoulder	Large	Test QS 1064, QS 755 and QS 532	5 all	5	4	NS	No improvement	No	8y 4m
43	18y,M	Forearm	Medium	Test QS 755	5	5	4	NS	No improvement	No	2y 7m
44	40y,F	Arm	Large	Test QS 755 and QS 532	5 both	5	4	NS	No improvement	No	2y 3m
45	18y,M	Arm	Large	Test QS 755 and QS 532	5 both	5	4	NS	No improvement	No	3y 9m
46	19y,F	Arm	Large	QS 755 (1)	5	-	4	NS	No improvement	No	3y 8m
47	38y,F	Hip	Large	Test QS1064, QS532, QS755 and LP755	5 all	5	4	NS	No improvement	No	8y 3m
48	13y,M	Thorax	Large	Test QS 755 and QS 532	5 both	5	4	NS	No improvement	No	5y 3m
49	16y,M	Flank	Large	Test QS 1064, QS 755 and QS 532	5 all	5	4	NS	No improvement	No	8y 10m
50	29y,F	Abdomen	Large	Test QS 755 and QS 532	5 both	5	4	NS	No improvement	No	3y 3m
51	20y,M	Arm	Large	Test QS ruby	5	5	4	NS	No improvement	No	10y 1m
52	17y,M	Arm	Medium	Full treatment QS755 (2) Test QS 532	3 4	5 5	4 4	NS	Complete	No	1y 11m
53	61y,M	Scapular	Medium	Test QS 532, QS 755	5	-	4	NS	No improvement	No	1y
54	36y,M	Scapular	Large	Full treatment QS755 (2) Test QS 1064, QS 532	3 5 both	5 5	4	NS	Complete	No	7y 8m
55	15y,F	Thigh	Large	Test QS 755, QS 532	6 both	5 both	4	NS	No improvement	No	2y 6m

Table 3. Continued.

Patients		Lesion		Treatment	Results						Follow-up
N	Age, gender	Site	Size	Type (and number of sessions)	PGA-ST	PGA-LT	Patients' self evaluation	Patients satisfaction	Recurrence	Scar	
56	26y,F	Shoulder	Large	QS 755 (4)	2	1	-	-	No	No	1y
57	13y,M	Shoulder	Large	Test QS 755	5	-	-	-	No improvement	No	-
58	20y,F	Shoulder	Large	Test QS1064, QS755, QS 694, QS 532	5 all	-	-	-	No improvement	No	-
59	17y,F	Thorax	Large	Test QS 1064, QS 755, QS 532	5 all	-	-	-	No improvement	No	-
60	15y,M	Cheek	Small	Test QS 1064, QS 755	5 both	-	-	-	No improvement	No	-
61	37y,F	Breast	Large	Test QS 755, QS 532	5 both	-	-	-	No improvement	No	-
62	30y,M	Face	Large	Test QS 1064, QS 755, QS 532	5 all	-	-	-	No improvement	No	-
63	22y,F	Arm	Large	Test QS 755, QS 532	5 both	-	-	-	No improvement	No	-
64	16y,M	Thorax	Large	Test QS 755, QS 532	5 both	-	-	-	No improvement	No	-
65	18y,M	Cheek	Large	Test QS 755, QS 532	5 both	-	-	-	No improvement	No	-

PGA-ST= Short Term-Physician Global Assessment; PGA-LT= Long Term-Physician Global Assessment; VS= Very Satisfied; S= Satisfied; NS= Not Satisfied

Table 4. Characteristics and results of other rare types of epidermal nevi treated with laser

Patients		Lesion		Treatment	Results						Follow-up
N	Age, gender	Site	Size	Type (and number of sessions)	PGA-ST	PGA-LT	Patients' self evaluation	Patients satisfaction	Recurrence	Scar	
ILVEN											
66	51y,M	Right trunk and leg	Large	Verrocous: CO2 (8) Erythematous: PDL (3)	2	2	3	S	Partial	No	3y
67	61y,M	Pretibil	Small	Erythematous: PDL (3)	2	Absent	2	S	No	No	2y
RAVEN											
68	15y,F	Shoulder	Small	Er YAG (1)	4	5	4	NS	Complete	No	5y 4m
Nevus Lipomatosus Superficialis											
69	28y,F	Buttocks	Small	CO2 (1)	2	4	3	S	Partial	No	2y 6m
Smooth Muscles Hamartoma											
70	18y,F	Cheek	Medium	PDL (1)	3	3	-	-	Yes	No	5y 5m

ILVEN= Inflammatory Linear Verrucous Epidermal Nevus; RAVEN= Rounded And Velvety Epidermal Nevus; PGA-ST= Short Term-Physician Global Assessment; PGA-LT= Long Term-Physician Global Assessment; S= Satisfied; NS= Not Satisfied

Almost all VEN were treated with CO2 or Er:YAG ablative lasers. Only two patients had hyperpigmented thin VEN, and were thus treated with Q-switched lasers. Among the 23 patients with VEN, only 4 (17%) patients showed moderate, poor or no improvement. Two patients (8.7%) had a short-term PGA of 0, and 16 patients (69.6%) had 1 and 2, eight patients each; resulting in 18 patients with good to complete improvement. Seven of them (39%) showed partial or complete recurrence (Table 5). After a follow-up which ranged between 12 and 106 months (mean 45.2 months, median 37 months), three patients had a poor response, two with no response, and one worsened. The remaining 16 patients (69.6%) kept an improvement of more than 50%. At the last follow-up, fourteen patients (82%) were still satisfied or very satisfied with the treatment results.

Table 5. Verrucous epidermal nevus and nevus sebaceous treatment response, recurrence and long-term patient satisfaction

	Patients	Recurrence	Scar	Satisfaction: n (%)		
PGA-ST	n	n (%)	n (%)	Very Satisfied	Satisfied	Not satisfied
VEN						
Good response	18	7 (39)	6 (33)	4	12	2
Poor or no response	4	3 (75)	1 (25)	0	3	1
Absent PGA-ST	1	1	0	0	0	1
Total	23	11 (48)	7 (30)	4 (17.4)	15 (65.2)	4 (17.4)
NS						
Good response	8	7 (88)	3 (38)	2	4	2
Poor or no response	8	7 (88)	3 (38)	1	2	5
Total	16	14 (88)	6 (38)	3 (18.8)	6 (37.5)	7 (42.8)

VEN= Verrucous Epidermal Nevus; NS= Nevus sebaceous; PGA-ST= Short Term-Physician Global Assessment

* The only patient without PGA-ST was lost to follow-up from the laser treatment until more than 8 years later

16 patients were treated for NS. Eight (50%) showed an initial improvement of more than 50%. However, 14 patients (88%) had partial or complete recurrence at long-term follow-up, but half of them were satisfied with the temporary or partial improvement. The follow-up period ranged from 13 to 127 months (mean 45 months, median 36 months).

26 patients were treated with QS laser for their Becker nevi. For each one of them, a test session was initially performed on one to four areas using different wavelengths, including 1064 nm, 755 nm, 694 nm, and 532 nm (total number of treated areas: 56). Only three patients (5.4%) experienced any degree of improvement, which was slight to moderate in two of them with complete recurrence soon after. The third had a good to excellent improvement after four sessions of QS 755 nm laser without recurrence, but with a relatively short follow-up of 12 months.

Some rare forms of EN are presented in Table 4. Two cases of ILVEN showed 50-89% improvement, mainly with PDL laser on the erythematous parts of the lesion. The only case of RAVEN, or acanthosis nigricans-like epidermal nevus, was slightly improved with Er:YAG ablative laser with a rapid and complete recurrence. A nevus lipomatosus superficialis was treated successfully with CO2 laser, yet the lesion partially recurred two years later. The last case shows a partial improvement of the erythema of a smooth muscle hamartoma with a PDL.

Discussion

In the present long-term follow-up study we found a differential response pattern to laser therapy based on the type of epidermal nevus. Verrucous epidermal nevus patients exhibited more than 50% improvement in 81.8% of them, mainly with ablative lasers. After a mean follow-up of 45.2 months, success rate remained high with 16 good responders out of the 22 patients evaluated (72.7%). Accordingly, 78.3% of these patients graded their improvement as good, almost cleared or cleared with a satisfaction rate of 82.6% after a mean follow-up of more than 3 years. These results corroborate those of Alonso *et al.* with good results in 93% of VEN patients. Nevertheless, they reported a lower recurrence rate (20%) than in our study (50%) but a higher rate of hypopigmentation or scarring (46.6%) than in our study (27%).[11] This might be explained by a more superficial ablation in our practice, differences in the follow-up, or by recording minor recurrences in our study. Thual *et al.* have also demonstrated a good response in 86% of their 21 patients and a recurrence rate of 38% with a short follow-up of 7 and 11 months for some patients.[13] Both articles agreed that thickness of VEN is not predictive of poor response, which conforms to our observations. Park *et al.* achieved good results in 15 out of 20 patients treated with the Er:YAG laser, with a recurrence rate of 25%, without any scar after a follow-up of two years.[14] A randomized controlled study revealed 100% success, 0% recurrence, and 50% scarring or dyspigmentation with pulsed CO2 laser compared to 90% success, 30% recurrence, and 10% dyspigmentation with pulsed Er:YAG laser. However, the only significant difference was the shorter healing time with Er: YAG.[7] In our series, we didn't observe a statistical difference in terms of recurrence comparing the use of Er:YAG to CO2 laser (p=0.5).

Regarding NS, only eight patients (50%) had more than 50% improvement. 88% of them (7/8) showed some degree of recurrence and 38% developed permanent scars. Among the 16 NS patients, only two patients did not experience recurrence, but one of them had a superficial scar. The recurrence rate of NS was 90% for patients treated in Nice and 83% for Amsterdam, compared to 50% and 40%, respectively, for VEN (without statistical differences between the two centres for the two types of EN). The potential bias associated to the difference between operators did not alter our results. The reason

is that each type of EN had the same outcome in both centres, regardless of the treating physician. In both NS and VEN, many recurrences appeared beyond the first year. This highlights the importance of the long-term follow-up after treating these lesions.

We believe that the increased rate of recurrence and scarring in NS, compared to VEN, is related to the histological differences between them. NS is mainly a dermal lesion whose main components are sebaceous glands, immature hair follicles, and sweat glands with sometimes additional epidermal anomalies, while VEN is purely epidermal (keratinocytic) with acanthosis, papillomatosis and hyperkeratosis.[4] Thus, VEN can be removed completely or almost completely with excellent cosmetic outcomes, whereas recurrence is expected in NS when treating only the superficial part, and scarring is unavoidable if one tries to treat deeply the dermal part. Yet, partial improvement of NS lesions can be achieved but patients need to realize the high risk of scarring and recurrence. For both types, we don't recommend treating with aggressive laser settings or trying to treat the whole thickness deep into the dermis in one session. To avoid disfiguring scars, it is wise to treat first until the superficial or papillary dermis, and later if necessary the remaining deeper parts. We recommend to perform several passes to first flatten the lesion, then to decrease if necessary the power for the last passes to avoid treating too deeply in the dermis. Targeting a cosmetically acceptable scar could be the considered as the endpoint to avoid recurrence. Our results support this for the deeper lesions such as NS. However, most patients treated in our study for VEN did not developed scar or dyspigmentation as they were not treated too deeply. Thus, all of them have remnants of their lesions (PGA-LT = 1 or more). Interestingly, although the clearance was not complete, long term results remain good and most of the patients were satisfied or very satisfied at the long-term evaluation. Regarding the site and size of the lesions, we did not find any significant association with the degree of improvement. However, the only two hand VEN did not respond very well, and three out of the four non-satisfied VEN patients were treated for neck VEN. This might be explained be the high mobility of the treated areas which could alter the healing process.

When evaluating the populations of the above mentioned studies together with our patients, 53 VEN patients were treated only with CO2 lasers (different modes and parameters) and 42 patients with Er:YAG lasers. A total of 21 patients (39.6%) developed scars or permanent hypo or hyperpigmentation after CO2 lasers versus 6 patients (14.3%) after Er: YAG lasers ($p=0.006$). The thermal effect of CO2 laser might be the origin of these side effects. We cannot exclude a potential bias linked to the procedural differences between the different physicians, but the only controlled comparative study was in favor of this difference, although not significant, with a small number of participants. In our study, there was almost no difference as 25% of the patients had scarring or hypopigmentation with Er:YAG versus 28.6% with CO2.

Regarding Becker nevus, our study reveals that pigmentary lasers, regardless of their wavelengths, are not effective in treating the hyperpigmentation. Three patients (11.5%) experienced any degree of improvement. Only one of them (3.8%) maintained the improvement, after 4 sessions of QS 755 nm, but with a relatively short follow-up of 12 months. These results argue against the use of lasers for treating the pigmentary component of Becker nevus. Of note, none of our patients was treated with both hair removal and QS lasers. Thus, it is impossible to say if combining the two procedures would improve these results. Picosecond lasers do not seem to bring any advantage compared to QS nanosecond lasers as the only case report so far showed poor efficacy.[31] Interestingly, an Er:YAG laser was reported to be superior to QS 1064nm. A success rate of 100% was obtained without recurrence at two years [36] . Such promising data were corroborated recently with 50% of good responders and without recurrence at 1 year.[28] However, these data need to be confirmed in larger series.

The 2 ILVEN patients reported improvement with PDL for erythema and CO2 laser for the verrucous component, with partial recurrence in one of them. We already reported the successful treatment of ILVEN with the Er:YAG laser, with a partial recurrence after 6 months.[44] Two small case series demonstrated that ILVEN has a recurrence rate of 60 to 80% after being treated with a CO2 laser.[11,19]

The main limitations of our study are its retrospective nature and the lack of histological confirmation of the diagnosis in most of the patients. However, in most cases, the diagnosis of EN is easy and remains clinical. Although retrospective, the study was conducted in two university hospitals having large experience in treating medical conditions with lasers, and all the treatments were performed by only 3 physicians, thus reducing the variability linked to physician experience. Moreover, only 8 patients were completely lost to follow-up, and the 70 remaining could be contacted for assessing the long-term evolution. Our results also emphasize the need of an international long-term registry for these rare lesions treated with lasers to better assess the success rates, long term efficacy, side effects, and patient reported outcomes.

Conclusion

Our study shows that ablative lasers can achieve good cosmetic results in verrucous epidermal nevi with a high rate of good to excellent immediate outcome and a low rate of long term recurrences. In contrast, nevus sebaceous has a strong tendency to recur, and to develop a scar when treating deeply. In Becker nevus, Q-switch lasers didn't provide any benefit in almost all patients and should not be considered anymore for treating the hyperpigmented component of such epidermal nevi.

References

1. Brandling-Bennett HA, Morel KD. Epidermal nevi. *Pediatr Clin North Am*. 2010;57(5):1177-1198. doi:10.1016/j.pcl.2010.07.004
2. Ersoy-Evans S, Sahin S, Mancini AJ, Paller AS, Guitart J. The acanthosis nigricans form of epidermal nevus. *J Am Acad Dermatol*. 2006;55(4):696-698. doi:10.1016/j.jaad.2006.01.026
3. Bergonse FN, Cymbalista NC, Nico MM, et al. Giant nevus lipomatosus cutaneus superficials: case report and review of the literature. *J Dermatol*. 2000;27(1):16-19.
4. Asch S, Sugarman JL. Epidermal nevus syndromes. *Handb Clin Neurol*. 2015;132:291-316. doi:10.1016/B978-0-444-62702-5.00022-6
5. Fox BJ, Lapins NA. Comparison of treatment modalities for epidermal nevus: a case report and review. *J Dermatol Surg Oncol*. 1983;9(11):879-885.
6. Levi A, Amitai DB, Mimouni D, Leshem YA, Arzi O, Lapidoth M. Picosecond 532-nm neodymium-doped yttrium aluminum garnet laser-a promising modality for the management of verrucous epidermal nevi. *Lasers Med Sci*. 2018;33(3):597-601. doi:10.1007/s10103-017-2427-z
7. Osman MAR, Kassab AN. Carbon dioxide laser versus erbium:YAG laser in treatment of epidermal verrucous nevus: a comparative randomized clinical study. *J Dermatol Treat*. 2017;28(5):452-457. doi:10.1080/09546634.2016.1255305
8. Bhat YJ, Hassan I, Sajad P, et al. Evaluation of Carbon Dioxide Laser in the Treatment of Epidermal Nevi. *J Cutan Aesthetic Surg*. 2016;9(3):183-187. doi:10.4103/0974-2077.191646
9. López V, López I, Ricart JM. Successful carbon dioxide laser treatment for verrucous epidermal nevi on the nipple. *Dermatol Surg Off Publ Am Soc Dermatol Surg Al*. 2013;39(12):1936-1937. doi:10.1111/dsu.12337
10. Lapidoth M, Israeli H, Ben Amitai D, Halachmi S. Treatment of verrucous epidermal nevus: experience with 71 cases. *Dermatol Basel Switz*. 2013;226(4):342-346. doi:10.1159/000350938
11. Alonso-Castro L, Boixeda P, Reig I, de Daniel-Rodríguez C, Fleta-Asín B, Jaén-Olasolo P. Carbon dioxide laser treatment of epidermal nevi: response and long-term follow-up. *Actas Dermosifiliogr*. 2012;103(10):910-918. doi:10.1016/j.adengl.2012.10.001
12. Paradela S, Del Pozo J, Fernández-Jorge B, Lozano J, Martínez-González C, Fonseca E. Epidermal nevi treated by carbon dioxide laser vaporization: a series of 25 patients. *J Dermatol Treat*. 2007;18(3):169-174. doi:10.1080/09546630701335180
13. Thual N, Chevallier J-M, Vuillamie M, Tack B, Leroy D, Dompmartin A. [CO2 laser therapy of verrucous epidermal nevus]. *Ann Dermatol Venereol*. 2006;133(2):131-138.
14. Park J-H, Hwang E-S, Kim S-N, Kye Y-C. Er:YAG laser treatment of verrucous epidermal nevi. *Dermatol Surg Off Publ Am Soc Dermatol Surg Al*. 2004;30(3):378-381.
15. Pearson IC, Harland CC. Epidermal naevi treated with pulsed erbium:YAG laser. *Clin Exp Dermatol*. 2004;29(5):494-496. doi:10.1111/j.1365-2230.2004.01579.x
16. Boyce S, Alster TS. CO2 laser treatment of epidermal nevi: long-term success. *Dermatol Surg Off Publ Am Soc Dermatol Surg Al*. 2002;28(7):611-614.
17. Verma KK, Ovung EM. Epidermal and sebaceous nevi treated with carbon dioxide laser. *Indian J Dermatol Venereol Leprol*. 2002;68(1):23-24.
18. Alam M, Arndt KA. A method for pulsed carbon dioxide laser treatment of epidermal nevi. *J Am Acad Dermatol*. 2002;46(4):554-556.

19. Michel JL, Has C, Has V. Resurfacing CO2 laser treatment of linear verrucous epidermal nevus. *Eur J Dermatol EJD*. 2001;11(5):436-439.

20. Kaufmann R, Hibst R. Pulsed Erbium:YAG laser ablation in cutaneous surgery. *Lasers Surg Med*. 1996;19(3):324-330. doi:10.1002/(SICI)1096-9101(1996)19:3<324::AID-LSM7>3.0.CO;2-U

21. Hohenleutner U, Wlotzke U, Konz B, Landthaler M. Carbon dioxide laser therapy of a widespread epidermal nevus. *Lasers Surg Med*. 1995;16(3):288-291.

22. Hohenleutner U, Landthaler M. Laser therapy of verrucous epidermal naevi. *Clin Exp Dermatol*. 1993;18(2):124-127.

23. Ratz JL, Bailin PL, Wheeland RG. Carbon dioxide laser treatment of epidermal nevi. *J Dermatol Surg Oncol*. 1986;12(6):567-570.

24. Lee HE, Park SB, Lee JH, Im M. Nevus sebaceous treated with fractional carbon dioxide laser followed by pulsed dye laser. *Indian J Dermatol Venereol Leprol*. 2014;80(5):478-480. doi:10.4103/0378-6323.140336

25. Chung BY, Han SS, Kim BW, Chang SE, Lee MW. Effective treatment of congenital melanocytic nevus and nevus sebaceous using the pinhole method with the erbium-doped yttrium aluminium garnet laser. *Ann Dermatol*. 2014;26(5):651-653. doi:10.5021/ad.2014.26.5.651

26. Kiedrowicz M, Kacalak-Rzepka A, Królicki A, Maleszka R, Bielecka-Grzela S. Therapeutic effects of CO2 laser therapy of linear nevus sebaceous in the course of the Schimmelpenning-Feuerstein-Mims syndrome. *Postepy Dermatol Alergol*. 2013;30(5):320-323. doi:10.5114/pdia.2013.38363

27. Ashinoff R. Linear nevus sebaceus of Jadassohn treated with the carbon dioxide laser. *Pediatr Dermatol*. 1993;10(2):189-191.

28. Al-Saif F, Al-Mekhadab E, Al-Saif H. Efficacy and safety of short-pulse erbium: Yttrium aluminum garnet laser treatment of Becker's nevus in Saudi patients: A pilot study. *Int J Health Sci*. 2017;11(3):14-17.

29. Wulkan AJ, McGraw T, Taylor M. Successful treatment of Becker's Nevus with long-pulsed 1064-nm Nd:YAG and 755-nm alexandrite laser and review of the literature. *J Cosmet Laser Ther Off Publ Eur Soc Laser Dermatol*. May 2017:1-4. doi:10.1080/14764172.2017.1326613

30. Balaraman B, Friedman PM. Hypertrichotic Becker's nevi treated with combination 1,550 nm non-ablative fractional photothermolysis and laser hair removal. *Lasers Surg Med*. 2016;48(4):350-353. doi:10.1002/lsm.22465

31. Chan JC, Shek SY, Kono T, Yeung CK, Chan HH. A retrospective analysis on the management of pigmented lesions using a picosecond 755-nm alexandrite laser in Asians. *Lasers Surg Med*. 2016;48(1):23-29. doi:10.1002/lsm.22443

32. Piccolo D, Di Marcantonio D, Crisman G, et al. Unconventional use of intense pulsed light. *BioMed Res Int*. 2014;2014:618206. doi:10.1155/2014/618206

33. Meesters AA, Wind BS, Kroon MW, et al. Ablative fractional laser therapy as treatment for Becker nevus: a randomized controlled pilot study. *J Am Acad Dermatol*. 2011;65(6):1173-1179. doi:10.1016/j.jaad.2010.07.049

34. Choi JE, Kim JW, Seo SH, Son SW, Ahn HH, Kye YC. Treatment of Becker's nevi with a long-pulse alexandrite laser. *Dermatol Surg Off Publ Am Soc Dermatol Surg Al*. 2009;35(7):1105-1108. doi:10.1111/j.1524-4725.2009.01195.x

35. Glaich AS, Goldberg LH, Dai T, Kunishige JH, Friedman PM. Fractional resurfacing: a new therapeutic modality for Becker's nevus. *Arch Dermatol*. 2007;143(12):1488-1490. doi:10.1001/archderm.143.12.1488

36. Trelles MA, Allones I, Moreno-Arias GA, Vélez M. Becker's naevus: a comparative study between erbium: YAG and Q-switched neodymium:YAG; clinical and histopathological findings. *Br J Dermatol*. 2005;152(2):308-313. doi:10.1111/j.1365-2133.2004.06259.x

37. Trelles MA, Allones I, Vélez M, Moreno-Arias GA. Becker's nevus: Erbium:YAG versus Q-switched neodimium:YAG? *Lasers Surg Med*. 2004;34(4):295-297. doi:10.1002/lsm.20033

38. Moreno Arias GA, Ferrando J. Intense pulsed light for melanocytic lesions. *Dermatol Surg Off Publ Am Soc Dermatol Surg Al*. 2001;27(4):397-400.

39. Nanni CA, Alster TS. Treatment of a Becker's nevus using a 694-nm long-pulsed ruby laser. *Dermatol Surg Off Publ Am Soc Dermatol Surg Al*. 1998;24(9):1032-1034.

40. Kopera D, Hohenleutner U, Landthaler M. Quality-switched ruby laser treatment of solar lentigines and Becker's nevus: a histopathological and immunohistochemical study. *Dermatol Basel Switz*. 1997;194(4):338-343. doi:10.1159/000246131

41. Tse Y, Levine VJ, McClain SA, Ashinoff R. The removal of cutaneous pigmented lesions with the Q-switched ruby laser and the Q-switched neodymium: yttrium-aluminum-garnet laser. A comparative study. *J Dermatol Surg Oncol*. 1994;20(12):795-800.

42. Nelson JS, Applebaum J. Treatment of superficial cutaneous pigmented lesions by melanin-specific selective photothermolysis using the Q-switched ruby laser. *Ann Plast Surg*. 1992;29(3):231-237.

43. Tan OT, Morelli JG, Kurban AK. Pulsed dye laser treatment of benign cutaneous pigmented lesions. *Lasers Surg Med*. 1992;12(5):538-542.

44. Hammami Ghorbel H, Lacour J-P, Passeron T. Treatment of inflammatory linear verrucous epidermal nevus with 2940 nm erbium fractional laser. *J Eur Acad Dermatol Venereol JEADV*. 2014;28(6):824-825. doi:10.1111/jdv.12268

45. Conti R, Bruscino N, Campolmi P, Bonan P, Cannarozzo G, Moretti S. Inflammatory linear verrucous epidermal nevus: why a combined laser therapy. *J Cosmet Laser Ther Off Publ Eur Soc Laser Dermatol*. 2013;15(4):242-245. doi:10.3109/14764172.2013.807115

46. D'Antuono A, Balestri R, Zauli S, et al. Carbon dioxide laser: first-line therapy in vulvar inflammatory linear verrucous epidermal nevus. *Dermatol Ther*. 2012;25(1):92-94. doi:10.1111/j.1529-8019.2012.01429.x

47. Ulkur E, Celikoz B, Yuksel F, Karagoz H. Carbon dioxide laser therapy for an inflammatory linear verrucous epidermal nevus: a case report. *Aesthetic Plast Surg*. 2004;28(6):428-430. doi:10.1007/s00266-004-0024-6

48. Sidwell RU, Syed S, Harper JI. Pulsed dye laser treatment for inflammatory linear verrucous epidermal naevus. *Br J Dermatol*. 2001;144(6):1267-1269.

49. Molin L, Särhammar G. Perivulvar inflammatory linear verrucous epidermal nevus (ILVEN) treated with CO2 laser. *J Cutan Laser Ther*. 1999;1(1):53-56.

50. Alster TS. Inflammatory linear verrucous epidermal nevus: successful treatment with the 585 nm flashlamp-pumped pulsed dye laser. *J Am Acad Dermatol*. 1994;31(3 Pt 1):513-514.

CHAPTER 6

A Ultrafine particle concentrations during laser hair removal: Effectiveness of smoke evacuators

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Abstract

Background and Objectives: Laser smoke is a biohazard that contains potentially dangerous toxic and biological components. In laser hair removal (LHR), practitioners undergo prolonged exposure since this procedure is widely used without protective measures. Little is known about the effect of smoke evacuators on ultrafine particle concentrations during LHR. This study aims to assess the effect of different laser devices and different smoke evacuators on the ultrafine particle concentrations in the room during LHR.

Study design/ Materials and Methods: In a prospective observational study we included patients with skin photo types 2-4 for 755 nm alexandrite LHR at two study sites, receiving treatment in axillae and pubic area. Ultrafine particle concentrations were measured during LHR for two different alexandrite lasers, with and without an external smoke evacuator. Moreover, we assessed a device for LHR with a smoke evacuator integrated into the handpiece. Primary outcomes were the concentration of ultrafine particles (0.2-0.3 μm) per m^3 at one minute after initiation of treatment and maximum concentrations.

Results: A total of 15 patients were recruited for routine LHR. Without smoke evacuator, already at one minute after treatment onset, ultrafine particle concentrations rapidly increased. Both external and integrated smoke evacuators were highly effective with 3.7 - 7-fold decrease in maximal particle count. Similarly, maximal particle concentrations remained low with both smoke evacuators. At both study sites particle concentrations decreased slowly (8 minutes for 50% reduction) when treatment stopped.

Conclusion: LHR procedures generated an increase of ultrafine particles. Both the external and integrated smoke evacuators are highly effective in controlling ultrafine particle concentrations during LHR. Once particle concentrations are elevated and process had been completed, clearance of ultrafine particles is rather slow.

Introduction

Surgical smoke is a biohazard that contains potentially dangerous toxic and biological components [1-6]. This smoke is produced in clinically relevant quantities by various procedures in dermatology using lasers, electrosurgical techniques and ultrasound scalpels [6].

During the past years, a growing body of literature recognizes that surgical smoke causes harm following inhalation [5-7,9,10]. The diffusivity of particulate matter in surgical smoke depends on its size, with smaller particles having greater diffusivity than larger ones. Insoluble fine particulate matter with a diameter smaller than 2.5 μm reach the alveolar region of the lung, where the only clearance mechanism consists of phagocytosis by alveolar macrophages [10].

Various chemicals have been found in surgical smoke such as benzene, formaldehyde, acrolein, CO and hydrogen cyanide [5,6]. Furthermore, it has been shown that vital viruses are present in surgical smoke and depending on the size can deposit in the bronchioles and alveoli [6,9-11]. Data from several studies suggest that exposure to these toxic and biological compounds may be associated with Increased cardiovascular mortality, lung cancer and cardiopulmonary risks [9-13].

Over the years, laser hair removal (LHR) has become one of the most commonly used laser treatments in dermatology. Therefore, practitioners undergo prolonged exposure to laser smoke since this procedure is widely used without any protective measures [3,4].

Recently, a 755/1064 nm laser system has been developed that combines a smoke evacuator and cold air cooling that are both integrated in the hand piece. Potentially, such a system could minimize the release of smoke while allowing the comfort of cold air cooling. Few studies, however, have studied the actual effectiveness of different smoke evacuators in a real clinical setting, with contradictory results. [1,5,7]. Moreover, a laser combining a smoke evacuator and cold air cooling in the hand piece has never been assessed for particle concentrations in the laser room.

Therefore, the aim of this study is to assess and compare the effect of different laser devices and different smoke evacuators on the ultrafine particle concentrations in the laser room during LHR.

Materials and Methods

Patients

For this prospective observational study we recruited participants undergoing LHR at the department of dermatology located at the Amsterdam University Medical Center (AUMC) and Huid Medisch Centrum (HMC). Two alexandrite lasers were used according to standard operating procedures. To limit variation in smoke production we included only subjects with skin photo types 2-4 receiving 755 nm alexandrite laser treatment in axillae and pubic areas. Enrollment occurred from February 2019 to April 2019.

Procedures

The skin surface was shaved prior to the treatment and the fluence and pulse duration were chosen depending on skin type, location and hair morphology. The SquareEpil/SplendorX (Lumenis Inc, Santa Clara, CA, USA) was used at the location HMC and the GentleLase (Syneron Candela, Wayland, MA, USA) at AUMC. We refer to these alexandrite lasers as AlexS and AlexG, respectively. In both study sites the 755 nm wavelength was used at similar repetition rates and spot sizes. The hand piece of the AlexS is equipped with cold air cooling (based on Zimmer cold air cooling) combined with a built-in smoke evacuator with a suction capacity of at least 50 m^3/h (Fig. 1). The AlexG is equipped with cryogen skin cooling (dynamic cooling device) but without an integrated smoke evacuator. Therefore, the LN 100 series (TBH, Baden-Württemberg, Germany) with maximum suction capacity of 220 m^3/h was used as an external smoke evacuator device at both study sites. The distance between the tube of the external smoke evacuator and the treated skin was maintained within a range of 10 cm.

Measurements for both laser devices were collected under different room conditions. The room size of the locations are 60.6 m^3 (AUMC) and 45 m^3 (HMC). Both locations had a room ventilation of 8-fold air supply. One practitioner performed all procedures at both locations. In each procedure we assessed the ultrafine particle concentrations every minute during 5 minutes. In two procedures, we continued these measurements after the laser treatment stopped for a total of 14 minutes.

Written informed consent was received prior to the procedure from the practitioner and all patients. This study was exempted from full ethical approval because of the low burden and risk to the patient (W19-069).

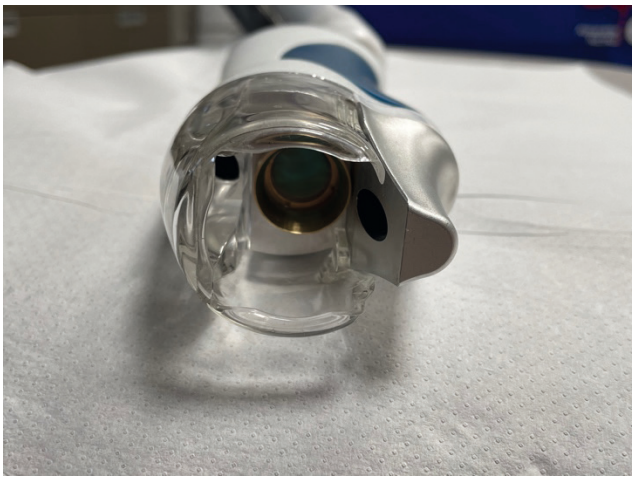

Figure 1. The hand piece of the integrated device is equipped with cold air cooling combined with a built-in smoke evacuator.

Measurements

To assess laser induced smoke under various conditions, we measured ultrafine particle concentrations during LHR for two different laser devices with and without smoke evacuators (table 1). Furthermore, we investigated whether the cryogen spray (AlexG) itself increases ultrafine particles to ensure that it could not bias results of smoke particle measurements. Therefore, we measured ultrafine particle concentrations generated by the cryogen skin cooling system only (no laser hair removal procedure and no smoke evacuator). During this procedure, we assessed the ultrafine particle concentrations in response to only cryogen spray pulses on the skin with a frequency of 1 Hz. We measured concentrations at baseline, after 1.0 minute and after 3.5 minutes.

Table 1. Study design with fifteen LHR procedures divided over five groups for measurement of smoke particle concentrations.

	AlexS	**AlexG**
Study Site	HMC	AUMC
Integrated smoke evacuator	3 patients	X
External smoke evacuator	3 patients	3 patients
No smoke evacuator	3 patients	3 patients

To imitate the position of the practitioner we placed the particle counter at one meter distance from the treatment area at head-height at both study sites.

Concentrations of ultrafine particles between 0.2-0.3 μm were detected using the Handheld 2016 airborne particle counter (Lighthouse Worldwide Solutions Benelux). The

Handheld 2016 is able to detect particles from 5 µm down to 0.2 µm. We differentially counted the number of particles between 0.2µm and 0.3µm in diameter as these aerosols particularly reach the lower respiratory tract and alveoli [10]. The Handheld 2016 identifies particles by a photo detector based upon either light scattering or light blocking. The amplitude of the light scattered or light blocked allows for sizing and counting individual particles.

Statistical Analysis

Our main outcomes were the average particle concentrations in each treatment group at 1 minute and the maximal concentrations. In each group 3 participants were assessed and we calculated the mean particle concentrations per time point. Descriptive analysis *was performed* using Excel 2016.

Results

A total of 15 patients were recruited for the LHR procedure. In the HMC, 9 patients received LHR with the AlexG. In the AUMC, 6 patients received LHR. The age of the patients ranged from 15 to 48 years (mean age 29 years). The average duration of LHR procedure in HMC was 3 minutes and 24 seconds. In the AUMC, the average duration of the LHR procedure was 3 minutes and 54 seconds. Demographics and laser parameters in the AUMC and HMC for individual patients are presented in table 2a and table 2b, respectively.

The average increase of particle concentrations of 3 treatments with 3 different patients at minute 1 during LHR in each group is shown in Figure 2a and Figure 2b. In both locations, the particle concentrations were the highest for the laser procedure without smoke evacuator. The groups with smoke evacuators show much lower particle concentrations for both the AlexG and AlexS. The mean increase of particle concentrations for the cryogen spray cooling system only (no laser pulses) was 736061.00/m^3 at minute 1 and 1504473/m^3 at 3.5 minutes.

Table 2a. Summary of demographics and laser parameters in the AUMC, CS=cryogen spray cooling, CA= Cold air cooling.

Site	Laser	Skin type	Sex	Fluence	Spotsize	Pulse duration ms	Repetition Rate Hz	Cooling
AUMC	AlexG	2-4	F	17	18	3	1,0	CS

Table 2b. Summary of demographics and laser parameters in HMC, CS=cryogen spray cooling, CA= Cold air cooling.

Site	Laser	Skin type	Sex	Fluence	Spotsize	Pulse duration ms	Repetition Rate Hz	Cooling
HMC	AlexS	2-4	F	14	20	5	1,5	CA

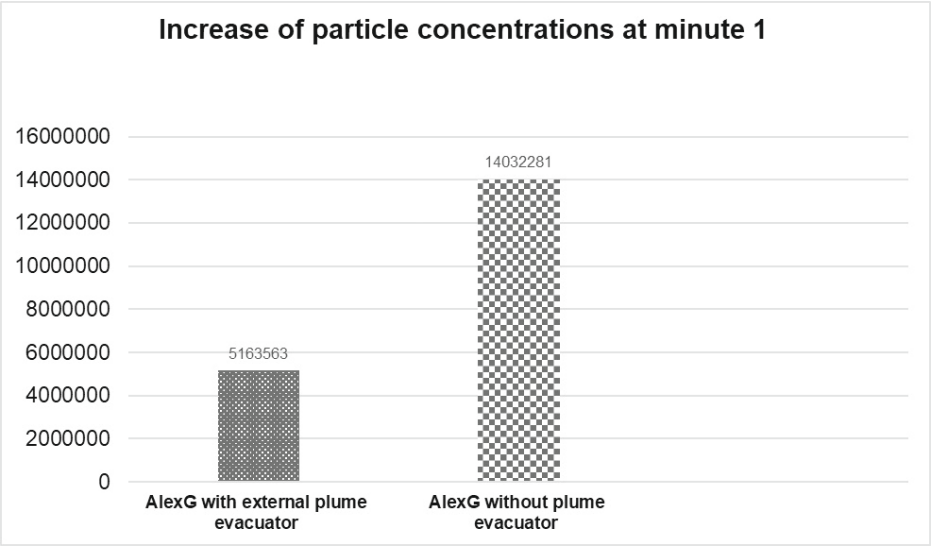

Figure 2a. Particles per cubic meter measured at one minute after onset of LHR of AlexG at the AUMC location. Each bar is the increase of particles/m^3 from baseline to minute 1 and represents the average of 3 treatments in 3 patients

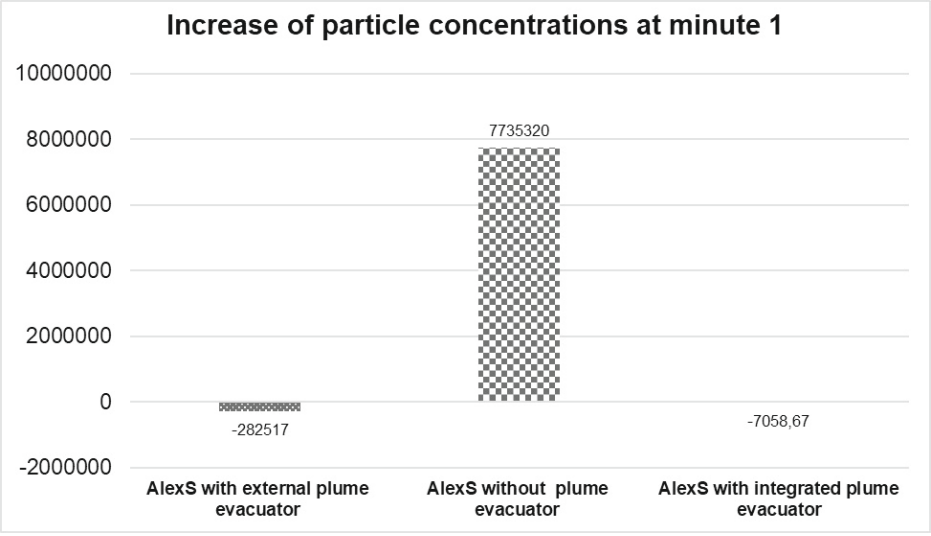

Figure 2b. Particles per cubic meter measured at one minute after onset of LHR of AlexS at HMC location. Each bar is the increase of particles/m^3 from baseline to minute 1 and represents the average of 3 treatments in 3 patients

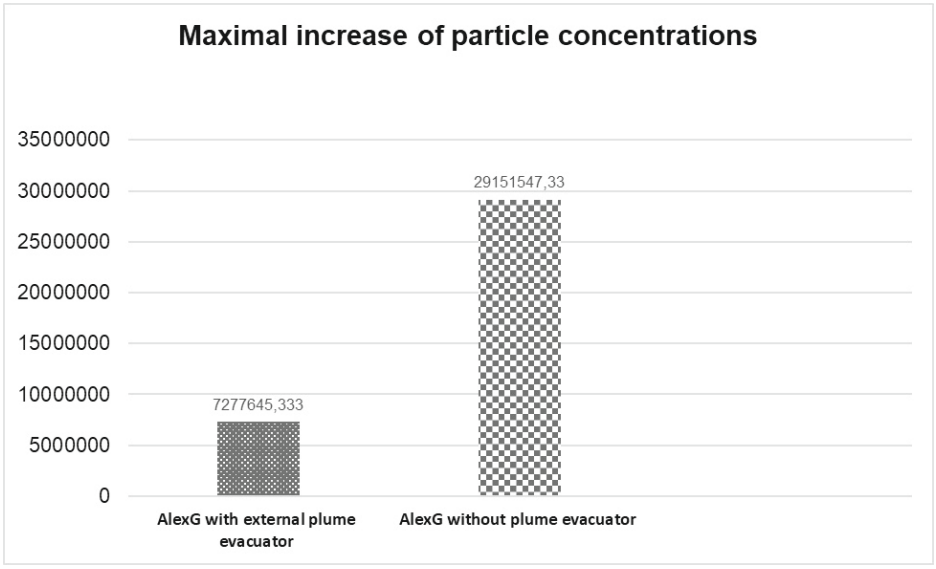

Figure 3a. Particles per cubic meter measured at maximum concentration after onset of LHR of AlexG at the AMC location. Each bar is the increase of particles/m^3 from baseline to minute 1 and represents the average of 3 treatments in 3 patients

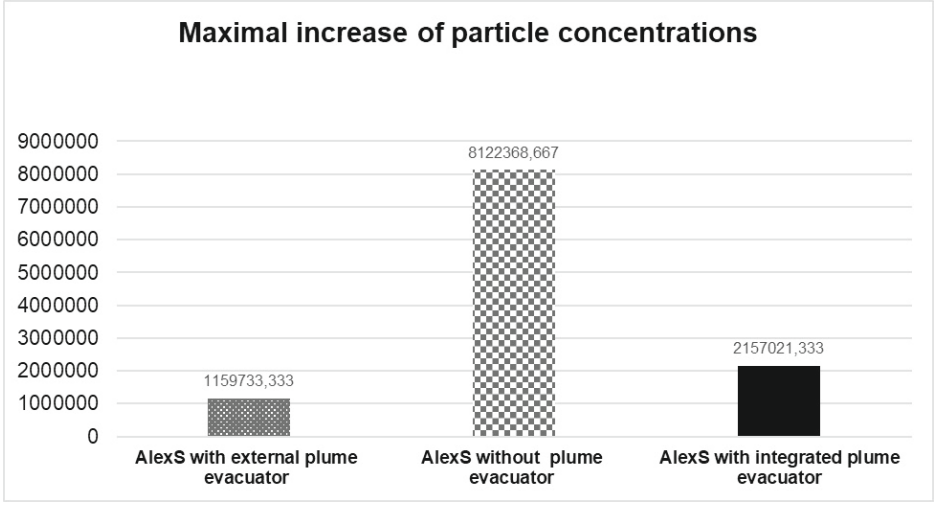

Figure 3b. Particles per cubic meter measured at maximum concentration after onset of LHR of AlexS at HMC location. Each bar is the increase of particles/m^3 from baseline to minute 1 and represents the average of 3 treatments in 3 patients

Similarly, the maximal concentrations of particles during LHR were the highest for the groups without smoke evacuators and for the AlexG with cryogen cooling (Fig. 3a). Again, concentrations of particles were low for the groups with smoke evacuators. For the AlexG, the external smoke evacuator reduced the maximal particle counts by a factor of 4. For the AlexS, the external smoke evacuator reduced the maximal particle count by a factor of 7 (Fig.3b). The integrated smoke evacuator reduced the maximal particle counts by a factor of 3.7 (Fig. 3b).

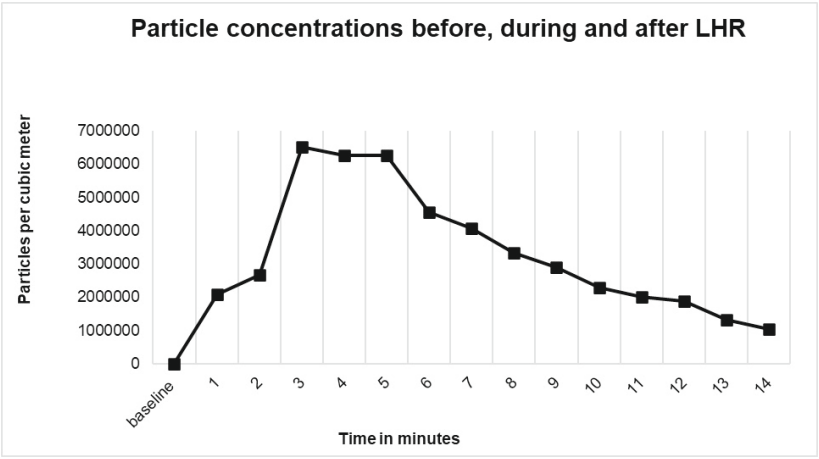

Figure 4a. Particle concentration (particles sized 0.2-0.3 µm/m^3) illustrated over time at the study site of AlexG in AUMC from a single treatment. The red box represents the duration of the LHR procedure. Plume evacuation started at baseline and stopped when stopped after 5 minutes.

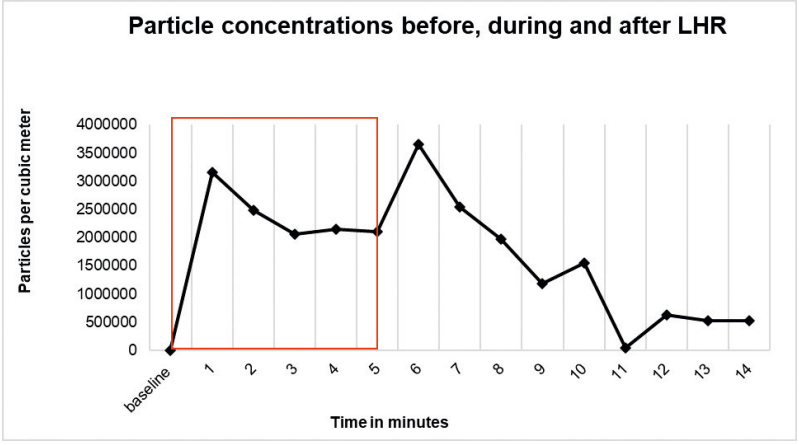

Figure 4b. Particle concentration (particles sized 0.2-0.3 µm/m^3) illustrated over time at the study site of AlexS in HMC from a single treatment. The red box represents the duration of the LHR procedure. Plume evacuation started at baseline and stopped when stopped after 5 minutes.

Discussion

Although laser smoke has been recognized as a potential health risk for decades, previous studies were mostly limited to the identification or description of the problem. This study aimed to assess the effect of various laser devices and different smoke evacuators on the ultrafine particle concentrations in the procedure room during routine LHR.

In our study, we observed a substantial increase in ultrafine particle concentrations during LHR procedures. These findings are consistent with results published by Ross et al., Chuang et al. and Eshleman et al., which demonstrate that LHR procedures generate very high concentrations of ultrafine particles [1,5,7]. Although our study focused on measuring the concentrations of particles in single LHR procedures, the study of Ross et al. focused on single and sequential LHR procedures in the laser room. Their study confirms that highest levels of ultrafine particles are reached after treating several patients sequentially, which reflects the real clinical setting [1]. The study of Eshleman et al. found that the mean concentration of particles was 2.89 times greater during the procedure and 2.09 times greater after the procedure as compared to background ultrafine particle concentrations [7]. Moreover, Chuang et al. demonstrated an 8-fold increase of particle concentrations as compared to the ambient room baseline level during LHR [5].

We observed that the external and integrated smoke evacuator were both highly effective, in preventing the increase in ultrafine particle concentrations. Nevertheless, the maximal concentration with the external plume evacuator is lower, in comparison with the integrated plume evacuator. This may result from the higher maximum suction capacity of the external stand-alone smoke evacuator (220 versus 50 m^3/h).

We used an external plume evacuator with a combination of a HEPA filter and activated carbon filter that traps particles as small as 0.12 μm and a precipitator efficiency of 99.95%. for 0.1 - 0.3 μm particles. While there are filters such as the ULPA filters with a higher filtration capacity (>99.99%), the efficiency of particle evacuation will also depend on the power of the suction capacity of the device, its ability to produce a threshold minimum volume of airflow and the distance of the nozzle to the treated skin. [15,16] In line with these results, a study by Seipp et al. reported that portable smoke evacuators can reduce surgical smoke up to 99%. Additionally, their study demonstrates that a cutting angle of 45°, the maximum suction capacity and a flow rate of 10,500 $m^{e/h}$ are optimal conditions for evacuators' efficacy [17].

Although it may not be standard practice, all the subjects in this study shaved hair prior to laser treatment. Without shaving, particle concentrations may be substantially higher [18]. The distance to the treatment area seems an important factor in the use of smoke evacuators. In the study of Eshleman et al., the smoke evacuator was placed 30.5 cm away from the skin [7]. Their study reported no substantial decrease of ultrafine

particle concentrations. However, considerable effect was seen in our data when using the external smoke evacuator within 10.0 cm from the skin. According to Chuang et al.,the velocity of the particles being drawn to the smoke evacuator drops with the fourth power of distance away from the suction source [5]. Their suggestion is to place the evacuator within 5.0 cm from the site of smoke generation. However, for a single operator, it is not feasible to perform LHR and simultaneously adjust the distance of the smoke evacuator within a range of 5 cm of the treatment area. Only a smoke evacuator integrated in the hand piece allows for such a very short distance.

Furthermore, type of surface cooling seems to affect the generation of ultrafine particles. We detected an increase of ultrafine particle due to the cryogen spray cooling system itself. This may explain the finding that LHR with the cryogen spray cooling system (AlexG) produced an increased level of detectable ultrafine particles, in comparison to LHR with the cold air cooling (AlexS). This finding is in line with a study of Ross et al. who found that LHR performed with either sapphire contact cooling or cold air cooling produced significantly less laser smoke than treatments with cryogen spray cooling. Some studied suggested that cryogen spray cooling produces a sudden airflow which likely disperses the ultrafine particles, whereas other types of surface cooling produce less airflow. It is therefore important to position the evacuator in close proximity of the spray [5,7].

The COVID-19 pandemic has raised the attention to potential viral transmission resulting from medical procedures and the role of aerosols. Consequently, there is an increased focus on personal protective measures in health care. However, opposed to procedures involving human epithelial cells of the upper or lower respiratory tract, plasma or serum, laser induced smoke from the skin will contain relatively small amounts of SARS-CoV-2 particles of which the relevance for transmission is unknown. In skin, HPV transmission is probably of higher concern[19,20]. Nevertheless, treatments around the mouth or the nose have an increased risk due to a higher viral load on the skin surface and the long survival of 9 hours of SARS-CoV-2 on the skin [21].Several guidelines by the WHO and local dermatological societies give recommendations on how to minimize potential risks of transmission [20].

Consistent with previous literature, we also perceived that the decline of ultrafine particles following the LHR treatment is rather slow [5,7]. Prolonged use of PPE is therefore necessary to protect practitioners from inhaling smoke after finishing treatment.

Strengths of this study are the standardized conditions for skin type, wavelength, body region and operator. 'A limitation of this study are differences in laser settings (fluence, spotsize, pulse duration and repetition rate), which may influence the results. Moreover, differences in the laser rooms may also influence the results. Therefore, a direct comparison of the plume generation by AlexS and AlexG is not possible.

Conclusion

In conclusion, laser hair removal generates high concentrations of ultrafine particles which are known as potential health hazard. Utilizing either form of evacuation, external and integrated, during LHR procedures significantly reduced the number of ultrafine particles. Once particle concentrations are elevated, decline is rather slow. Therefore, physicians are encouraged to use additional methods to minimize the number of ultrafine particles during, and after LHR procedures.

References

1. Ross EV, Chuang GS, Ortiz AE, Davenport SA. Airborne particulate concentration during laser hair removal: A comparison between cold sapphire with aqueous gel and cryogen skin cooling. Lasers Surg Med. 2018;50(4):280-3.
2. Pierce JS, Lacey SE, Lippert JF, Lopez R, Franke JE, Colvard MD. An assessment of the occupational hazards related to medical lasers. J Occup Environ Med. 2011;53(11):1302-9.
3. Alp E, Bijl D, Bleichrodt RP, Hansson B, Voss A. Surgical smoke and infection control. J Hosp Infect. 2006;62(1):1-5.
4. Aleem S, Majid I. Unconventional Uses of Laser Hair Removal: A ReviewJ Cutan Aesthet Surg. 2019 Jan-Mar; 12(1): 8–16.
5. Chuang GS, Farinelli W, Christiani DC, Herrick RF, Lee NC, Avram MM. Gaseous and Particulate Content of Laser Hair Removal Plume. JAMA Dermatol. 2016;152(12):1320-6.
6. Barrett WL, Garber SM. Surgical smoke: a review of the literature. Is this just a lot of hot air? Surg Endosc. 2003;17(6):979-87.
7. Eshleman EJ, LeBlanc M, Rokoff LB, Xu Y, Hu R, Lee K, et al. Occupational exposures and determinants of ultrafine particle concentrations during laser hair removal procedures. Environ Health. 2017;16(1):30.
8. Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation. 2010;121(21):2331-78.
9. Taravella MJ, Viega J, Luiszer F, Drexler J, Blackburn P, Hovland P, et al. Respirable particles in the excimer laser plume. J Cataract Refract Surg. 2001;27(4):604-7.
10. Searle T, Ali FR, Al-Niaimi F, Surgical plume in dermatology: an insidious and often overlooked hazard. Clin. Exp. Dermatol.2020:1-7
11. Lewin JM, Brauer JA, Ostad A. Surgical smoke and the dermatologist. J. Am. Acad. Dermatol. 2011;65(3):636-
12. Wolf K, Schneider A, Breitner S, Meisinger C, Heier M, Cyrys J, et al. Associations between short-term exposure to particulate matter and ultrafine particles and myocardial infarction in Augsburg, Germany. Int J Hyg Environ Health. 2015;218(6):535-42.
13. Karottki DG, Beko G, Clausen G, Madsen AM, Andersen ZJ, Massling A, et al. Cardiovascular and lung function in relation to outdoor and indoor exposure to fine and ultrafine particulate matter in middle-aged subjects. Environ Int. 2014;73:372-81.
14. Derrick JL, Li PT, Tang SP, Gomersall CD. Protecting staff against airborne viral particles: in vivo efficiency of laser masks. J Hosp Infect. 2006;64(3):278-81. 15. Schultz, L. An Analysis of Surgical Smoke Plume Components, Capture, and Evacuation. AORN J. 201. doi:10.1016/j.aorn.2013.07.020
16. Georgesen, C., Lipner, S. R. Surgical smoke: Risk assessment and mitigation strategies. J. Am. Acad. Dermatol. 2018. doi:10.1016/j.jaad.2018.06.003
17. Seipp HM, Steffens T, Weigold J, Lahmer A, Maier-Hasselmann A, Herzog T, Herzog-Niescery J. Efficienies and noise levels of partable surgical smoke evacuation systems. J. Occup. Environ. Hyg.2018;15(11):773-781.
18. Casey AS, Goldberg D, Guidelines for laser hair removal. J Cosmet Laser Ther. 2008 Mar;10(1):24-33.

19. Cembrano, K., Ng, J. N., Rongrungruang, Y., Auewarakul, P., Goldman, M. P., Manuskiatti, W. COVID-19 in dermatology practice: getting back on track. LasersMed Sci.2020;35(8), 1871–1874. 20. Elsaie, M. L., Nada, H. A. Insights into laser safety considerations during COVID 19 pandemic. Dermatol. Ther. (2020). 21. Hirose R, Ikegaya H, Naito Y, Watanabe N, Yoshida T, Bandou R, Daidoji T, Itoh Y, Nakaya T. Survival of SARS-CoV-2 and influenza virus on the human skin: Importance of hand hygiene in COVID-19. Clin Infect Dis. 2020 Oct 3:ciaa1517. doi: 10.1093/cid/ciaa1517.

CHAPTER 7

Laser-induced smoke in dermatologic practice: A survey to explore hazard perceptions, safety measures and unmet needs

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Abstract

Background: Inhalation of laser-induced smoke is a potential health hazard to exposed physicians and laser operators. To date, little is known about the perception of health hazards related to laser-induced smoke exposure among physicians and the actual use of safety measures to mitigate these risks.

Objective: To assess current perceptions of health hazards of laser-induced smoke and its management among members of the European Society for Lasers and Energy Based Devices (ESLD).

Methods: In May 2020, 514 members of the ESLD were invited by email to participate in an online survey. The survey comprised 16 questions including multiple choice and open-ended questions.

Results: Responses were received from 109 participants. The majority (90%) were aware of potential hazards and highlighted a desire for better protective measures (60%). A smoke evacuation system was frequently used with ablative lasers (66%) and fractional ablative lasers (61%), but less the case with non-ablative laser (30%) and hair removal lasers (28%). The COVID-19 outbreak had no clear effect on the use of smoke evacuation systems. Prior to the COVID-19 outbreak, mainly surgical masks were used (40-57%), while high filtration masks (FFP1, FFP2 or FFP3) were used by only a small percentage (15-30%). Post COVID-19 outbreak, the use of high filtration masks increased significantly (54-66%), predominately due to an increase of use the of FFP2 masks Reasons mentioned for inadequate protective measures were sparse knowledge, limited availability, discomfort, excessive noise, high room temperatures and financial costs.

Conclusion: While there is considerable awareness of the hazards of laser-induced smoke among physicians and laser operators, yet a substantial number do not use appropriate protective measures. Implementation of regulations on safety measures is hampered by sparse knowledge, limited availability, discomfort, excessive noise, financial issues, and high room temperatures.

Introduction

With technical progress and increasing numbers of procedures in dermatologic practice, the use of lasers and electrosurgery has markedly increased leading to repeated exposure of physicians to surgical smoke.[1,2]

A growing body of evidence shows that surgical smoke is a potential risk to physicians and laser operators.[3,4] Surgical smoke is generated when tissue is heated to the point of boiling. This leads to membrane rupture and dispersal of cellular contents as fine particles. Surgical smoke does not only contain burnt particles but also aerosols (<5µm) and liquid droplets (>5 µm) that are diffused.[5,6]

Substances of surgical smoke include toxic chemicals such as carbon monoxide, acrylonitrile, hydrogen cyanide and formaldehyde, in addition to biological and/or infectious components of human tissue.[7,8]

Approximately 75% of surgical smoke consists of small particles between 0.07 and 0.31 µm, which may quickly deposit in bronchioles and alveoli.[9,10] Dose-dependent health complaints linked to inhalation of surgical smoke include headache, nausea, rhinitis, burning sensation in the nasopharynx, as well as more serious conditions such as asthma or pneumonia.[10,11] Respiratory irritation, possible carcinogenesis, and infectious transmission are the most commonly mentioned (and feared) hazards associated with inhalation of surgical smoke.[12-14] As previous studies demonstrate the presence of different viruses in surgical smoke, such as human papillomavirus (HPV), the onset of COVID-19 has highlighted the risk of potential virus transmission.[15]

There are currently no uniform regulations across different countries for laser procedures in dermatologic practice in the setting of COVID-19.[15,16] Although there are guidelines for respiratory protection at the workplace in many countries, these safety procedures are not generally adopted.[17,18] Moreover, guidelines are mainly designed for and implemented in the operating room rather than in private practice where most dermatologic procedures are performed on a daily basis.[19] As many institutions have not made the implementation of these guidelines rigorous, it is plausible that a substantial number of physicians and other health care workers are unaware of the health hazards of surgical smoke and subsequently fail to implement protective measures.[19,20]

To date, little is known about the perception of health hazards of laser-induced smoke among physicians and laser operators, and the actual use of safety measures to mitigate these risks. The primary aim of this study is to assess current perceptions of health hazards of laser-induced smoke among members of the European Society for Lasers and Energy Based Devices (ESLD). The secondary aim is to explore the actual use and the obstacles of protective measures in dermatologic practice. Additionally, the survey assesses the potential influence of the COVID-19 outbreak on the use of these protective measures.

Methods

Recruitment

For the purpose of this study, a survey was performed between May and June 2020. The survey was conducted online with a self-developed questionnaire comprising of 16 questions including multiple choice and open-ended questions. The board of the ESLD approved this questionnaire for distribution to its members (mainly dermatologists and plastic surgeons) in and outside of Europe.

The survey, distributed through Lime Survey, was emailed using the Society's mailing list (514 members at the time of implementation of this survey). The survey took approximately ten minutes to complete. Reminder emails were sent after three weeks. Responses were electronically stored in a database.

Survey Instrument and development

The questionnaire (appendix S1) was developed based on previous surveys that assessed perceptions of physicians towards (electro)surgical and laser-induced smoke.8,19,20 Additionally, we included new questions generated specifically for this study focusing on protective measures during different laser procedures.

The first section of the survey focused on respondent characteristics. The second and third sections covered perceptions about the awareness of health hazards of laser-induced smoke and the use of protective measures during various laser procedures. The laser procedures were classified into (1) ablative laser, (2) fractional ablative laser, (3) non-ablative laser (vascular, pigment, non-ablative fractional laser), and (4) hair removal laser. For each type of laser procedure, we questioned about the use of (1) protective masks, (2) the type of mask (surgical mask, high filtration mask including FFP1, FFP2 and FFP3), (3) smoke evacuation systems or (4) no protective equipment. FFP refers to Filtering Face Piece 1, 2 and 3, which is the European standard for high filtration masks with an increasing filtration efficiency of respectively 80%, 95% and 99% for particles of 0.3 μm. Surgical masks are not capable of filtering particulate matter <5 μm.21,22

Additionally, all these questions were asked referring to the situation before and after the COVID-19 outbreak.

In the last section of the survey, we questioned the obstacles (reasons for not using protective measures), preferences, and suggestions for improvement of equipment.

Quantitative survey items utilized 'yes/no' questions, multiple choice questions, and five-point Likert scales for the perception and obstacles concerning surgical smoke protection (1 = strongly disagree to 5 = strongly agree).

Qualitative survey items included free text responses.

Results

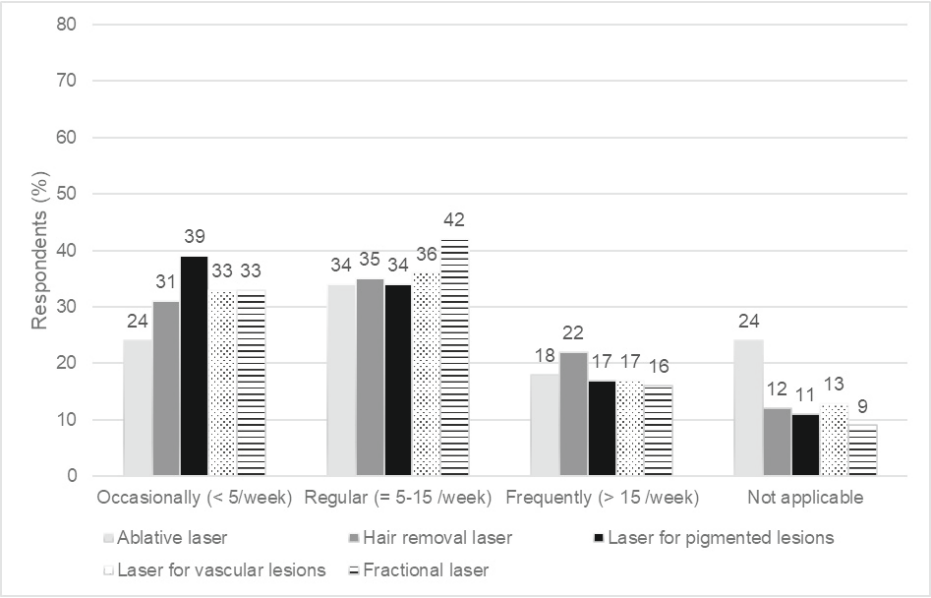
Respondent characteristics

A total of 514 members of the ESLD were invited by email. Responses were received from 109 (21.2%) members from 40 countries. The main characteristics of the respondents are reported in Table 1 and Figure 1.

Respondents were mainly dermatologists (81%) of which the majority came from Europe (57%). The majority was experienced to highly experienced (84%) with the use of lasers and had a private clinic as their primary practice setting (Table 1). The panel of respondents used a wide variety of different types of lasers on a regular basis (Figure 1).

Table 1. Respondent characteristics

	N (%)
Number of respondents, n (%):	109 (100)
Dermatologists	88 (81)
Aesthetic physicians	4 (4)
Plastic surgeons	3 (3)
Laser therapists/skin therapists	5 (5)
Other	9 (9)
Gender, n (%):	43 (39)
Male	64 (59)
Female	2 (2)
Not mentioned	
Country of current practice, n (%):	62 (57)
Europe	27 (25)
Asia	8 (7)
North America	5 (5)
South America	6 (6)
Other	
Years of experience with the use of lasers, n (%):	17 (16)
< 5	25 (23)
5-10	20 (18)
10-15	47 (43)
>15	
Major practice location, n (%):	17 (16)
Hospital	65 (60)
Private clinic	27 (24)
Both	



Awareness about the health hazards of surgical smoke

Almost all respondents (90%) agreed or strongly agreed that laser-induced smoke is a potential health hazard. In relation to their own working environment, 74% of the respondents indicated that health hazards of laser-induced smoke are already a topic of interest or concern among their team.

Use of protective measures in the workplace (before and after COVID-19 outbreak)

The data on the use of protective measures before and after the COVID-19 outbreak are listed in Table 2.Before the COVID-19 outbreak, a surgical mask was the most frequently used protective mask during laser procedures. Surgical masks were used in 40-57% of the procedures. These masks were used more frequently during ablative laser procedures (57%) than during fractional ablative procedures (48%), non-ablative laser procedures (42%) and hair removal laser procedures (40%). Post COVID-19 outbreak, the use of surgical masks decreased for all procedures except for non-ablative laser treatments (54%). High filtration masks (FFP1, FFP2 or FFP3) were used by only a small percentage before COVID-19. Their use depended on the type of procedure, being the highest in ablative lasers (30%) and the lowest in hair removal lasers (15%). Interestingly, post COVID-19 outbreak the use of high filtration masks increased significantly (54-66%), predominantly due to an increase of use of FFP2 masks with frequencies of 43% for both ablative and fractional-ablative procedures, 37% for non-ablative procedures, and 39% for hair removal laser procedures.

A smoke evacuation system was frequently used with ablative lasers (66%) and fractional ablative lasers (61%) but lesss the case in non-ablative lasers (30%) and hair removal lasers (28%). The COVID-19 outbreak had no clear effect on the use of smoke evacuation systems among our respondents. Remarkably, some respondents did not use any protective measure with ablative lasers (13%), fractional ablative lasers (11%), non-ablative lasers (26%) and hair removal lasers (24%). Post COVID-19 outbreak non-use of protective measures was much lower, respectively 4%, 3%, 11% and 8%.

Table 2. Summary of percentage of respondents using protective measures during laser procedures before and after COVID-19 outbreak

	Before COVID-19 outbreak (%)	After COVID-19 out break (%)
Ablative laser:	59 (57)	23 (22)
Surgical mask	9 (9)	12 (12)
FFP1 mask	11 (11)	45 (43)
FFP2 mask	10 (10)	11 (11)
FFP3 mask	69 (66)	68 (65)
Smoke evacuation system	14 (13)	4 (4)
No protection		
Fractional ablative laser:	49 (48)	25 (25)
Surgical mask	7 (7)	11 (11)
FFP1 mask	10 (10)	43 (43)
FFP2 mask	11 (11)	10 (10)
FFP3 mask	62 (61)	57 (56)
Smoke evacuation system	11 (11)	3 (3)
No protection		
Non-ablative laser*:	45 (42)	
Surgical mask	11 (10)	55 (54)
FFP1 mask	5 (5)	10 (10)
FFP2 mask	9 (8)	38 (37)
FFP3 mask	32 (30)	8 (8)
Smoke evacuation system	28 (26)	38 (37)
No protection		11 (11)
Hair removal laser:	39 (40)	34 (37)
Surgical mask	6 (6)	7 (8)
FFP1 mask	4 (4)	36 (39)
FFP2 mask	5 (5)	6 (7)
FFP3 mask	28 (28)	30 (33)
Smoke evacuation system	23 (24)	7 (8)
No protection		

FFP: Filtering Face Piece

*Non-ablative laser group consists of pigment, vascular, and non- ablative fractional laser procedures

Perceptions concerning use of safety measures

A total of 60% of the respondents stated they would like to have more or better protective measures concerning laser-induced smoke, although the majority of these 60% considered their taken safety measures as sufficient. Among the remainder who felt that they did not make sufficient use of safety measures, the three most common given reasons were: "*safety measures are not incorporated in our process yet", "the safety measures are distracting during the procedure", "the procedure time is too short/the smoke development is too low"*.

To increase the use of protective measures more knowledge on hazards of laser-induced smoke and protection was recommended. Respondents also indicated an increased need for FFP3 masks. Furthermore, according to their experience, more comfortable masks are needed. Masks should not be distracting during the laser procedure and nose and mouth should be covered without fogging the goggles, and blocking breathing. Additionally, respondents emphasized a demand for improved smoke evacuation systems (integrated in handpiece, automated positioning).

The noise of smoke evacuation systems was also reported as an obstacle for more frequent use of these systems. 72 % of all respondents agreed or strongly agreed that the noise of smoke evacuation systems is annoying/disturbing.

More than half of the respondents (53%) was concerned about hearing damage from continued exposure to noisy devices and 51% was disturbed by the increased room temperature due to lasers and smoke evacuation systems. Only 15% did not experience noise and increased room temperature as obstacles. Built-in protection equipment in laser devices is seen as an important facilitator during laser procedures. Ssuggestions included integration of a smoke evacuation system into the hand piece and a cooling system for stabilizing room temperature. The high cost of smoke evacuation systems was seen as a barrier and there was a preference for more durable evacuation systems in the future.

Discussion

This survey indicates that most physicians and laser operators who perform laser treatments are aware of laser-induced smoke hazards, yet a substantial number do not use appropriate protective measures such as smoke evacuation systems and/or high filtration masks during laser procedures. Overall, 60% of all respondents indicated they would desire more or better protective measures.

The study found that smoke evacuation systems were used by only 66% of those performing ablative laser treatment, which is remarkable given the high amount of generated smoke. As expected, a lower percentage of use of smoke evacuation systems were found with fractional ablative lasers (61%), non-ablative lasers (30%) and hair

removal lasers (28%). While laser-induced smoke is clearly visible and detected by repulsive odor in ablative laser procedures, smoke is also relevant in non-ablative procedures.[23] With hair removal lasers, a substantial increase of ultrafine particle concentration has been found in the laser room already one minute after starting the procedure. Smoke evacuation systems were able to limit the increase in ultrafine particles.[24]

Although it is known that surgical masks do not provide sufficient protection against ultrafine particles, they were often used with ablative lasers (57%), fractional ablative lasers (48%), non-ablative laser (42%) and hair removal lasers (40%). [17,19,20] Surgical masks do not filter particulate matter <5 μm and only confer little protection to the respiratory tract against aerosols and viral particles.[21] The common use of surgical masks is problematic when utilized in situations that require high filtration masks. On average, the protection factors of high filtration masks are 12 to 16 times greater than those of surgical masks.[25] According to Wizner *et al.,* physicians may not be aware about the selection of the adequate mask nor know the specific type of filtration mask they use.[26]

This study shows a substantial difference in the use of protective measures before and after the COVID-19 outbreak. Before the COVID-19 outbreak, predominantly surgical masks were used (40% – 57%), while FFP2 masks (4% - 11%) and FFP3 masks (5% - 11%) were less frequently used. Conversely, after the COVID-19 outbreak the high filtration masks played a more significant role especially in the use of FFP2 masks, increasing minimal fourfold for all procedures. Post COVID-19 outbreak, these FFP2 masks were used by about 40% of the respondents (Table 2). These changes probably reflect protective measures against primarily infection with the coronavirus rather than generic laser-induced smoke protection. Therefore, it is likely that once the COVID-19 pandemic has passed, the extra protective measures may be reversed or somewhat relaxed.

According to a survey by Edwards *et al.,* the inconsistent application of protective measures is due to differences in guidelines concerning the safe use of lasers.[27] In our study, the most cited reason for insufficient protection of participants was safety measures yet not being incorporated in the working procedures. These results are in line with a similar recent study by Michaelis *et al.* who concluded that changes in the standard working procedures with a focus on occupational health and safety are recommended in the future.[19]

In our study we also noted that physicians were concerned about distraction by masks during the laser procedures. This statement has also been found in previous studies on electrosurgical smoke.[2,10,28]

For example, physicians have difficulties with the fog effect while breathing in the mask or experience impaired vision. Other difficulties include the disturbing noise and increased room temperature produced by smoke evacuation systems and the absence of a smoke evacuation system integrated in the handpiece. In addition to practical concerns

on comfort, the cost of smoke evacuation systems and price difference between surgical masks and high filtration masks were also mentioned as obstacles for use of protective measures. Although no statistical analysis and uniform conclusions can be drawn from these comments, the findings warrant further research and adaptation in dermatologic practice.

There are some limitations to our study. We only surveyed ESLD members, which may limit the external validity of the study. The results may not apply to other laser physicians and users. Moreover, only one-fifth of the ESLD members responded (despite a reminder after three weeks) which may further contribute to a selection bias. In the future, it would be interesting to compare results from other groups of laser physicians.

In summary, this study indicates that many physicians do not use smoke evacuation systems and/or high filtration masks during laser procedures, and some physicians not even with ablative lasers. A more cautious approach was seen due to the COVID-19 outbreak. Despite awareness on the health hazards of laser-induced smoke, protective measures are not consistently implemented and are hampered by lack of knowledge, limited availability, financial costs, discomfort, excessive noise, and high room temperatures.

Therefore, we recommend first of all, international and national guidelines that will give guidance on the use of protective measures per type of laser procedure. Secondly, we advise more education on the risks of laser-induced smoke and the benefits of smoke evacuation systems and high filtrations masks for physicians and laser operators. Finally, we encourage technical changes to smoke evacuation systems and high filtration masks that make their use more comfortable and practical when performing laser treatments. Continuous feedback from physicians is of importance to target the barriers of use and to increase compliance with guideline recommendations.

References

1. Lewin, J. M., Brauer, J. A. & Ostad, A. Surgical smoke and the dermatologist. *Journal of the American Academy of Dermatology* (2011) doi:10.1016/j.jaad.2010.11.017.
2. Oganesyan, G., Eimpunth, S., Kim, S. S. & Jiang, S. I. B. Surgical smoke in dermatologic surgery. *Dermatologic Surg.* (2014) doi:10.1097/DSS.0000000000000221.
3. Liu, Y., Song, Y., Hu, X., Yan, L. & Zhu, X. Awareness of surgical smoke hazards and enhancement of surgical smoke prevention among the gynecologists. *Journal of Cancer* (2019) doi:10.7150/jca.31464.
4. Chuang, G. S. *et al.* Gaseous and particulate content of laser hair removal plume. *JAMA Dermatology* (2016) doi:10.1001/jamadermatol.2016.2097.
5. de Boorder, T., Verdaasdonk, R. & Klaessens, J. The visualization of surgical smoke produced by energy delivery devices: significance and effectiveness of evacuation systems. *Therm. Treat. Tissue Energy Deliv. Assess. IV* 6440, 64400R (2007).
6. Stahl, C. *et al.* Comparison of the Filtration Efficiency of Different Face Masks Against Aerosols. *Front. Med.* 8, 1–5 (2021).
7. Bree, K., Barnhill, S. & Rundell, W. The Dangers of Electrosurgical Smoke to Operating Room Personnel: A Review. *Work. Heal. Saf.* 65, 517–526 (2017).
8. Hensman, C., Baty, D., Willis, R. G. & Cuschieri, A. Chemical composition of smoke produced by high-frequency electrosurgery in a closed gaseous environment: An in vitro study. *Surg. Endosc.* (1998) doi:10.1007/s004649900771.
9. R., T., Y., L., B.J., C. & J.W., T. Recognition of aerosol transmission of infectious agents: A commentary. *BMC Infect. Dis.* (2019).
10. Golda, N., Merrill, B. & Neill, B. Intraoperative electrosurgical smoke during outpatient surgery: a survey of dermatologic surgeon and staff preferences. *Cutis* (2019).
11. Bigony, L. Risks Associated with Exposure to Surgical Smoke Plume: A Review of the Literature. *AORN J.* (2007) doi:10.1016/j.aorn.2007.07.005.
12. Tseng, H. S. *et al.* Cancer risk of incremental exposure to polycyclic aromatic hydrocarbons in electrocautery smoke for mastectomy personnel. *World J. Surg. Oncol.* (2014) doi:10.1186/1477-7819-12-31.
13. Limchantra, I. V., Fong, Y. & Melstrom, K. A. Surgical Smoke Exposure in Operating Room Personnel: A Review. *JAMA Surgery* (2019) doi:10.1001/jamasurg.2019.2515.
14. Chiang, Y. Z., Al-Niaimi, F., Ferguson, J., August, P. J. & Madan, V. Carbon dioxide laser treatment of cutaneous neurofibromas. *Dermatol. Ther. (Heidelb).* **2**, 1–6 (2012).
15. Mowbray, N. G. *et al.* Safe management of surgical smoke in the age of COVID-19. *British Journal of Surgery* (2020) doi:10.1002/bjs.11679.
16. Emadi, S. N. & Abtahi-Naeini, B. Coronavirus Disease 2019 (COVID-19) and dermatologists: Potential biological hazards of laser surgery in epidemic area. *Ecotoxicology and Environmental Safety* (2020) doi:10.1016/j.ecoenv.2020.110598.
17. Ball, K. Compliance with surgical smoke evacuation guidelines: Implications for practice. *AORN J.* (2010) doi:10.1016/j.aorn.2010.06.002.
18. Edwards, B. E. & Reiman, R. E. Comparison of Current and Past Surgical Smoke Control Practices. *AORN J.* (2012) doi:10.1016/j.aorn.2011.07.019.

19. Michaelis, M., Hofmann, F. M., Nienhaus, A. & Eickmann, U. Surgical smoke—hazard perceptions and protective measures in german operating rooms. *Int. J. Environ. Res. Public Health* 17, (2020).

20. Chapman, L. W., Korta, D. Z., Lee, P. K. & Linden, K. G. Awareness of surgical smoke risks and assessment of safety practices during electrosurgery among us dermatology residents. *JAMA Dermatology* (2017) doi:10.1001/jamadermatol.2016.5899.

21. Searle, T., Ali, F. R. & Al-Niaimi, F. Surgical plume in dermatology: an insidious and often overlooked hazard. *Clinical and Experimental Dermatology* (2020) doi:10.1111/ced.14350.

22. Hirschmann, M. T. *et al.* COVID-19 coronavirus: recommended personal protective equipment for the orthopaedic and trauma surgeon. *Knee Surgery, Sport. Traumatol. Arthrosc.* (2020) doi:10.1007/s00167-020-06022-4.

23. Eshleman, E. J. *et al.* Occupational exposures and determinants of ultrafine particle concentrations during laser hair removal procedures. *Environ. Heal. A Glob. Access Sci. Source* (2017) doi:10.1186/s12940-017-0239-z.

24. de Boer, A. J. A. & Fransen, F. Ultrafine particle concentrations during laser hair removal: Effectiveness of smoke evacuators. *Lasers Surg. Med.*(2021) doi: 10.1002/lsm.23465.

25. Li, K. K. W., Joussen, A. M., Kwan, J. K. C. & Steel, D. H. W. FFP3, FFP2, N95, surgical masks and respirators: what should we be wearing for ophthalmic surgery in the COVID-19 pandemic? *Graefe's Archive for Clinical and Experimental Ophthalmology* (2020) doi:10.1007/s00417-020-04751-3.

26. Wizner, K., Nasarwanji, M., Fisher, E., Steege, A. L. & Boiano, J. M. Exploring respiratory protection practices for prominent hazards in healthcare settings. *J. Occup. Environ. Hyg.* (2018) doi:10.1080/15459624.2018.1473581.

27. Edwards, B. E. & Reiman, R. E. Results of a Survey on Current Surgical Smoke Control Practices. *AORN J.* (2008) doi:10.1016/j.aorn.2007.11.001.

28. Ahmad, M., Mohmand, M. H. & Ahmad, T. A Survey among Plastic Surgeons Wearing a Mask in Operating Room. *WORLD J. Plast. Surg.* (2019) doi:10.29252/wjps.8.1.93.

CHAPTER 8

General Discussion

Part I: Development of the Generic Core Outcome Set (GOS) for the international Laser trEAtments in Dermatology (LEAD) registry

In the past decade, advances in laser technology resulted in promising therapeutic options with low risk of adverse events.(1) Laser treatment is frequently used in clinical practice for many uncommon or rare skin diseases.(2) Due to their low prevalence, the literature consists mostly of case reports and small uncontrolled case series. Unfortunately, case studies in laser dermatology do not allow for firm conclusions about the real benefit of these treatments.(3,4,5)

This thesis describes in the first section a platform that will enable laser clinicians to prospectively register relevant outcomes of laser treatments. Capturing data of uncommon and rare skin diseases in an international registry will increase both the sample sizes and the reliability of conclusions. The registry for Laser Treatments in Dermatology project, as described in **chapter 2,** is therefore a critical step, enabling adequate national and international collaboration between clinicians and researchers in this field. In contrast to clinical trials, patient registries aim to gather real-world evidence which reflect daily practice and the overall population.(6) However, a registry requires international collaboration and agreement about the 'core' data and outcomes that need to be collected, and the time points for data collection, in order to be able to combine the shared data. The use of a core outcome set (COS) in practices supports this endeavor.

Core outcome sets are already available for a great number of diseases in various medical disciplines and the importance is stressed by recognized entities in research. Since 1992, the Outcome Measures in Rheumatology (OMERACT) group and the COMET (Core Outcome Measures in Effectiveness Trials) group developed many Core Outcome Sets (COS) according to a framework and methodology (i.e. the OMERACT Filter).

For the development of the outcome domain set for the registry, we chose to follow the Core Outcome Set Initiative within the Cochrane Skin Group (CS-COUSIN), established in 2014, since they already made the development of COSs available for a great number of dermatological diseases. The COUSIN group has developed a practical guidance document on how to develop COSs based on the Harmonizing Outcome Measures for Eczema (HOME) roadmap, which was the first core outcome initiative set out in 2008.

Together with the Consortium for Harmonizing Outcomes Research in Dermatology (CHORD), the COUSIN group has formed a union organizational structure known as C^3: CHORD COUSIN Collaboration. A wide range of common and rare dermatologic conditions are represented by COS groups as part of C^3, such as HOME for atopic eczema, OVAMA for vascular malformations and OCOMEN for congenital melanocytic nevi. (7-20)

The development process of the outcome domain set for the LEAD registry consisted of two main phases described in the protocol (**chapter 2**):

1) a literature review to assess which outcomes are commonly used in the literature for laser treatments (**chapter 3**)
2) a consensus study according to the Delphi methodology (**chapter 4**).

This first section discusses the process of developing the outcome domain set and reflects on the findings of this thesis.

Definition of generic outcome set and classifying outcome domains.

During the past years, COSs in dermatology have been developed for a specific disease. However there has been no focus yet on a Generic Outcome Set (GOS), for a wide range of skin conditions.

The definition of the scope and the use of a GOS derived from the concept of COS was the first step during this thesis project. For example, do different types of laser interventions (e.g., vascular, pigmented, laser hair removal) for various dermatological diseases address different outcomes, requiring intervention-specific COSs? A COS is defined as an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials of a specific disease.(8, 10) However, with so many skin diseases involved, reaching consensus on core domains, core outcomes and measurement instruments for the purpose of the laser registry is very challenging. The concept of 'generalizability' of outcome domains to more than one disease is promising and useful in this context. This is in line with the results of a review by Schmitt et al. (2019) comparing outcomes in underlying clinical trials that provided thoughts on common domains applied to a range of diseases in dermatology.(11)

Given the time-consuming process of selecting core domains and measurement instruments, it is impossible to reach consensus on a COS for each skin condition apart. All the more as there are hundreds of uncommon dermatological conditions for which laser treatments have been published. We, therefore, started with the development and use of a 'generic' core outcome set (GOS) specifically for use in a registry on multiple laser interventions for various skin disorders. The rationale for the development of the GOS is supported by the fact that only a limited number of outcome domains has been used in research to report outcomes of various laser treatments in various skin disorders. Similarly, a limited number of outcome domains has identified in the existing disease-specific COSs in dermatology within CS-COUSIN.

A first attempt to provide a framework and resource for an extension of the general taxonomy of Dodd et al. (2018) to dermatology specifically has been made by Lange et a.(12) CS-COUSIN plans to further expand the current state of development to support

and accelerate the extension of a dermatology-specific taxonomy as a resource for study trialists, reviewers and COS developers.(13)

The review in this thesis, **chapter 3,** showed that in 150 studies, as much as 105 different outcomes were used. We allocated these outcomes according to the OMERACT 2.0 filter and COMET outcome domain taxonomy (12), since their filter has resulted in successful development and implementation of core domain and measurement sets for many different diseases. Regarding the classification of outcomes, we encountered the themes of description of outcomes, stakeholder involvement.

Description of outcomes

We noticed that many outcomes comprise very broad concepts such as 'improvement', 'clearance' or 'progression', but with either different or unclear underlying definitions, or even no definition at all. Considering the current outcome domains of the GOS, a deeper and more precise description of time of measurement (e.g..'3 weeks after treatment') of an outcome domain and analysis metric of the outcome domain (e.g., the occurrence, time of progression, severity, frequency, intensity or the complete remission) is needed in the future.

The use of a list of components to describe an outcome, which was proposed by OMERACT Filter 2.1 is very beneficial to define and categorize domains and outcomes. (19) However, in the future, we need a more detailed description of *what* to measure but also *how* to measure and *when* to measure. In order to reduce the diversity of terminologies used by different COS initiatives in the field dermatology, Lange et al. (2021) initiated a general taxonomy with definitions at different outcome domain levels.

Here, a bottom-up approach is used to provide a basis of mapped outcome domains for further development of a taxonomy for dermatology-specific diseases. Lange et al. emphasizes that components including measurement instruments, observer of outcome, time of measurement and analysis metrics are essential to optimize harmony in reporting. (13, 21) When using COSs and, in the light of the LEAD registry, a GOS, the component of *when* to measure outcomes is just as important as the components of *what* and *how* to measure.

Stakeholder involvement

The results of a Delphi study could be influenced by the composition of the panel. In this project, we aimed for a sample of experts that represent various international institutes, countries and continents, that demonstrates expertise in the field of laser dermatology. Following recommendations of COS guidance of CS-COUSIN(8), healthcare professionals were invited with expertise in the field of laser using the snowball method. This strategy resulted in a devoted group of experts with knowledge of the field, but smaller in size than initially planned, which is a limitation of the study. The geographical

range of experts, however, is an advantage from the perspective that we strived for international applicability of the GOS. The question remains whether involvement of a larger group of healthcare professionals would have resulted in a different GOS.

Future perspective of the international laser registry

Generic Outcome Measurement Set

In **chapter 3** we also found heterogeneity in measurement instruments to measure the selected outcomes for laser treatments. Most of the measurement instruments were not validated. Future studies should therefore focus on validation and selection of reliable and responsive measurement instruments. A generic outcome measurement set (GOMS) should therefore be developed as a next step, consisting of validated instruments to measure the generic outcome set for the diseases treated with lasers is necessary. However, for the use in a registry in daily practice properties like ease of use and feasibility are also essential.

With regard to the registry, it is suggested to find validated instruments per outcome domain with consensus methods. We suggest to follow the HOME roadmap or COSMIN guideline for selecting the most suitable outcome measurement instruments for clinical practice. (9, 20)

Extraction

One of the major challenges related with the development of outcome sets is ensuring impact, uptake and implementation. Although the importance of international collaboration in a registry is well known, the registration burden remains a point of discussion. The GOS is kept as small as possible and confined to collect the most relevant data for laser treatments. However, when using a limited number of outcomes for various skin disorders, it is probable that specific details of more complex diseases cannot be assessed. This limitation is inherent to the scope of a registry of multiple diseases. Also, on an international level, difference in registrations exist. To share best practices, the registry should include the same outcomes, outcome measurements in each country, preferably without free text field. This would facilitate automatic data extraction from the registry.

What do we aim for?

To date, there is no international registry for dermatological diseases treated with lasers. In **chapter 5,** the efficacy of ablative laser therapy for epidermal nevi is described in a retrospective cohort study involving centers of two countries. In this long-term follow-up study, we found a differential response pattern to laser therapy, based on the type

of epidermal nevus.(4) Moreover, due to the retrospective design, we were not able to assess all outcomes that are relevant and meaningful for the patient. The results of this study emphasize the need of an international long-term registry for these rare lesions treated with lasers. In the future, it is recommended to conduct studies with uncommon dermatological diseases with more international centers, choosing comparable outcomes and outcome instruments. Such a standardized documentation in the international LEAD registry may aid clinicians in choosing the optimal treatment for different indications, such as the treatment of epidermal nevi. In general, the LEAD registry is expected to aid in improved data collection on the success rates, long term efficacy, side effects, and patient reported outcomes of many similar uncommon dermatoses as described in **chapter 5**.

Part II: Laser Plume hazards and future perspectives

In the second part of this thesis, we focus on laser induced plume and discuss methods of control and perceptions among physicians. In **Chapter 6**, we assess the effect of different laser devices and different smoke evacuators on the ultrafine particle concentrations in the room during laser hair removal (LHR). Consistent with previous studies(22, 23) in our study we observed a substantial increase in ultrafine particle concentrations during LHR procedures. Furthermore, both external and integrated smoke evacuators were highly effective with a 3.7–7-fold decrease in maximal particle count. This is in contrast with findings from other studies, although differences in laser settings and rooms may have influenced results. In a study by Eshleman et al. (2017), the ultrafine particles did not decrease substantially with external smoke evacuation.(22) This discrepancy with our results may be explained by other factors such as the distance of the evacuator from the skin and the type of surface cooling. For laser induced smoke evacuation it is essential to trap the contaminant close to the source. Chuang et al. (2016) even suggests to place the evacuator within 5.0 cm from the site of plume generation, which is ensured by a smoke evacuator integrated into the handpiece of the laser.(23)

The findings of our study confirm the increase in ultrafine particles during LHR which deserves attention for the use of protection.(24) Moreover, it also raises interest whether these concentrations are similar to other laser procedures, such as vascular and pigmented laser treatments. The plume in LHR is generated from hair shaft carbonization. Interestingly, as seen in a survey among members of the European Society for Lasers and Energy Based Devices (ESLD), **Chapter 7,** a smoke evacuation system was frequently used for ablative - and fractional ablative lasers but rarely for non-ablative lasers. Information on ultrafine particle concentrations during other laser treatments is, to our knowledge, currently scarce or completely lacking.(25) Therefore, it is difficult

to compare the generation of ultrafine particles of the different commercially available devices. Future research should assess the concentrations of ultrafine particles in other types of laser treatments to create an overview of exposure to health care workers. The development of international and national guidelines is necessary to give guidance on the use of protective measures, such as smoke evacuation systems and/or high filtration masks per type of laser procedure.

In our study described in **chapter 7**, we also found that the majority of laser physicians were aware of potential hazards of laser-induced smoke. The acute and long-term risks of inhaling generated laser plume and the clinical significance on the long term is not known.(26) Previous relevant reviews about surgical smoke have identified potential health risks to physicians and other healthcare workers.(25, 26) These include respiratory irritation, the transmission of infectious and cancer cells, and genotoxicity. As long-term health risks are not adequately understood and still unknown, analysis of the contents of the plume together with long-term studies on exposure limits are needed and attention should continuously be paid to the preventive measures.(27) In line with other surveys on protective measures in surgical and electrosurgical smoke, the most cited reason for insufficient protection of participants was safety measures not being incorporated in the working procedures.(27, 28) However, we also found concerns among physicians due to discomfort, excessive noise, and high room temperatures when using safety measures. In the future, we should therefore pay attention that equipment in plume protection is more comfortable and practical when performing laser treatments.

Conclusion

This thesis aims to lay the foundation for an international registry, which is only the beginning of a change of data collection in the laser field. Further standardization of outcome measurements and international collaboration is essential. Also, the establishment of implementation of guidelines on safety measures during laser procedures is emphasized in this thesis. While there is awareness of the hazards of laser-induced smoke among physicians, implementation of regulations on safety measures is still hampered.

The available safety equipment can still be optimized. We found that local smoke evacuation systems and integrated smoke evacuators both decrease ultrafine particles in the laser room.

Finally, the recently developed generic outcome domain set for laser treatments represents a substantial step towards outcome standardization for various number of skin disorders. However, the real success lies in its implementation. The use of similar outcomes and outcome measurement instruments will need to be monitored in the

coming years. Meanwhile, advances in technology are needed for improving (automatic) data collection, patient information and monitoring and the implementation of generic outcomes, and feasibility of reporting these outcomes in the registry worldwide.

References

1. Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology: four decades of progress. J Am Acad Dermatol. 2003;49(1):1-31; quiz -4.
2. Alster TS, Lupton JR. Lasers in Dermatology. American Journal of Clinical Dermatology. 2001;2(5):291-303.
3. Gagne JJ, Thompson L, O'Keefe K, Kesselheim AS. Innovative research methods for studying treatments for rare diseases: methodological review. BMJ. 2014;349:g6802.
4. Alkhalifah A, Fransen F, Le Duff F, Lacour JP, Wolkerstorfer A, Passeron T. Laser treatment of epidermal nevi: A multicenter retrospective study with long-term follow-up. J Am Acad Dermatol. 2020;83(6):1606-15.
5. Fransen F, Tio D, Prinsen CAC, Haedersdal M, Hedelund L, Laubach HJ, et al. A systematic review of outcome reporting in laser treatments for dermatological diseases. J Eur Acad Dermatol Venereol. 2020;34(1):47-53.
6. Kolker S, Gleich F, Mutze U, Opladen T. Rare Disease Registries Are Key to Evidence-Based Personalized Medicine: Highlighting the European Experience. Front Endocrinol (Lausanne). 2022;13:832063.
7. Prinsen CAC, Spuls PI, Kottner J, Thomas KS, Apfelbacher C, Chalmers JR, et al. Navigating the landscape of core outcome set development in dermatology. J Am Acad Dermatol. 2019;81(1):297-305.
8. Kottner J, Jacobi L, Hahnel E, Alam M, Balzer K, Beeckman D, et al. Core outcome sets in dermatology: report from the second meeting of the International Cochrane Skin Group Core Outcome Set Initiative. Br J Dermatol. 2018;178(4):e279-e85.
9. Schmitt J, Apfelbacher C, Spuls PI, Thomas KS, Simpson EL, Furue M, et al. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. J Invest Dermatol. 2015;135(1):24-30.
10. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13:132.
11. Schmitt J, Lange T, Kottner J, Prinsen CAC, Weberschock T, Hahnel E, et al. Cochrane Reviews and Dermatological Trials Outcome Concordance: Why Core Outcome Sets Could Make Trial Results More Usable. J Invest Dermatol. 2019;139(5):1045-53.
12. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J Clin Epidemiol. 2018;96:84-92.
13. Lange T, Kottner J, Weberschock T, Hahnel E, Apfelbacher C, Brandstetter S, et al. Outcome assessment in dermatology clinical trials and cochrane reviews: call for a dermatology-specific outcome taxonomy. J Eur Acad Dermatol Venereol. 2021;35(2):523-35.
14. Thorlacius L, Ingram JR, Villumsen B, Esmann S, Kirby JS, Gottlieb AB, et al. A core domain set for hidradenitis suppurativa trial outcomes: an international Delphi process. Br J Dermatol. 2018;179(3):642-50.
15. Gerbens LAA, Apfelbacher CJ, Irvine AD, Barbarot S, de Booij RJ, Boyce AE, et al. TREatment of ATopic eczema (TREAT) Registry Taskforce: an international Delphi exercise to identify a core set of domains and domain items for national atopic eczema photo- and systemic therapy registries. Br J Dermatol. 2019;180(4):790-801.

16. Thiboutot DM, Layton AM, Chren MM, Eady EA, Tan J. Assessing effectiveness in acne clinical trials: steps towards a core outcome measure set. Br J Dermatol. 2019;181(4):700-6.

17. Horbach SER, van der Horst C, Blei F, van der Vleuten CJM, Frieden IJ, Richter GT, et al. Development of an international core outcome set for peripheral vascular malformations: the OVAMA project. Br J Dermatol. 2018;178(2):473-81.

18. Eleftheriadou V, Thomas K, van Geel N, Hamzavi I, Lim H, Suzuki T, et al. Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. Pigment Cell Melanoma Res. 2015;28(3):363-9.

19. Maxwell LJ, Beaton DE, Shea BJ, Wells GA, Boers M, Grosskleg S, et al. Core Domain Set Selection According to OMERACT Filter 2.1: The OMERACT Methodology. J Rheumatol. 2019;46(8):1014-20.

20. Prinsen CAC, Mokkink LB, Bouter LM, Alonso J, Patrick DL, de Vet HCW, et al. COSMIN guideline for systematic reviews of patient-reported outcome measures. Qual Life Res. 2018;27(5):1147-57.

21. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database--update and key issues. N Engl J Med. 2011;364(9):852-60.

22. Eshleman EJ, LeBlanc M, Rokoff LB, Xu Y, Hu R, Lee K, et al. Occupational exposures and determinants of ultrafine particle concentrations during laser hair removal procedures. Environ Health. 2017;16(1):30.

23. Chuang GS, Farinelli W, Christiani DC, Herrick RF, Lee NC, Avram MM. Gaseous and Particulate Content of Laser Hair Removal Plume. JAMA Dermatol. 2016;152(12):1320-6.

24. Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. Environ Int. 2020;143:105974.

25. Ilce A, Yuzden GE, Yavuz van Giersbergen M. The examination of problems experienced by nurses and doctors associated with exposure to surgical smoke and the necessary precautions. J Clin Nurs. 2017;26(11-12):1555-61.

26. Liu Y, Song Y, Hu X, Yan L, Zhu X. Awareness of surgical smoke hazards and enhancement of surgical smoke prevention among the gynecologists. J Cancer. 2019;10(12):2788-99.

27. Limchantra IV, Fong Y, Melstrom KA. Surgical Smoke Exposure in Operating Room Personnel: A Review. JAMA Surg. 2019;154(10):960-7.

28. Katoch S, Mysore V. Surgical Smoke in Dermatology: Its Hazards and Management. J Cutan Aesthet Surg. 2019;12(1):1-7.

CHAPTER 9

Summary

Laser treatments for skin diseases- Towards an international registry

This thesis consists of two main parts. The first part covers development of the Generic Core Outcome Set (GOS) for the international Laser trEAtments in Dermatology (LEAD) registry.

The second part discusses several aspects of safety, ranging from evaluating laser-induced smoke during laser hair removal treatments, to the perception and use of safety measures among physicians and the long-term effectiveness, and safety of lasers for epidermal nevi.

Part I: Development of the Generic Core Outcome Set (GOS) for the international Laser trEAtments in Dermatology (LEAD) registry

The rapid development of laser technology during the past decade resulted in the introduction of many new indications. Laser therapy has become an indispensable therapeutic modality in dermatology. This is reflected in the number of articles describing specific indications that are often labeled as orphan diseases in dermatology.

However, there is limited data on the role of laser treatments within the entire spectrum of dermatology, especially with regard to the effectiveness of therapy in uncommon skin disorders. Currently, laser studies measure whatever outcomes the individual researchers deem appropriate. An international registry may assist in collecting long-term effects and determining optimal laser treatment strategies, but they need to be developed and their data collection need to be standardized. A Core Outcome Set (COS), defined as a minimum set of oucomes that would be used in all clinical studies of a given disease or conditions, have the potential to make clincial research in laser devices results comparable, analyzable and more useful. Similar to the COS for clinical trials, it is important to develop COS for collecting data in daily practice for a registry. In dermatology, several COS are already developed for specific disorders. Since a wide variety of uncommon dermatological diseases is treated with lasers, a logical next step was to develop a Generic Outcome Set (GOS) determining 'what to measure' for the international Laser trEAtments in Dermatology (LEAD) registry.

A detailed protocol **in chapter 2** described the development process of the GOS consisting of two main phases: 1) a literature review to determine which outcomes are frequently used in research on laser treatments for a wide variety of medical indications and 2) a consensus study to agree on a generic outcome set for the LEAD registry according to the Delphi methodology.

In **chapter 3,** as the first step in the development of a generic outcome set for the LEAD registry, we undertook a systematic review to identify outcomes, outcome measurement instruments, methods and definitions reported in recently published literature of laser

treatments for skin disorders. Two researchers independently evaluated 150 studies including all types of studies involving laser treatments for the skin. There were 105 outcomes identified and categorized into eight domains recommended by the COMET framework: appearance, long-term effects, physician and patient-reported physical signs, satisfaction, health-related quality of life, psychological functioning and adverse events. Heterogeneity in outcome reporting (e.g. categories and outcome measurement instruments) was present, and definitions were insufficiently reported. Results of this review were used in the next step, the Delphi consensus, to reach consensus between stakeholders on the outcome domains to be implemented in the LEAD registry.

In **chapter 4 ,** we described the international e-Delphi consensus study involving three rounds to identify which generic outcome subdomains are most important to measure according to physicians and patients treated with lasers. A total of 26 generic outcomes were proposed to the participants. In phase three a face-to-face consensus meeting was conducted with 16 healthcare professionals and 16 patients in order to get consensus on the final generic outcomes (table 1) of which finally nine generic subdomain outcomes were extracted for the LEAD registry: Appearance of the skin disease assessed by physician, appearance of the disease assessed by patients, texture of the surface, color, affected surface area (size), overall quality of life, impact of disease/condition on physical activities of daily living, patient satisfaction with outcome, patient satisfaction with treatment, local adverse events (>6 months) and number of sessions. This resulted in the first international GDS for a registry on laser treatments based on an international Delphi study.

Table 1. Final GDS for the LEAD registry with 9 generic outcomes

Core area	Generic Outcome Domain	Generic outcome Subdomain **first level**	Generic outcome Subdomain **second level**
Physical/ clinical	*Signs as assessed by physician*	Appearance of the skin disease	Texture of the surface Color Affected surface area (size)
	Signs as assesd by patient	Appearance of the skin disease	
Life impact	*Quality of Life*	Overall QoL	Impact of diseze/condition on physical activities of daily living
	Satisfaction	Patient satisfaction with treatment	Patient satisfaction with outcome
	Adverse Events	Local adverse events (>6 months)	
	Delivery of care	Number of Sessions	

Part II: Laser Treatments and Safety in Clinical Practice

In **chapter 5** we present the results of a retrospective, cohort study, including all patients treated with, mostly ablative lasers for an epidermal nevus with more than a one-year follow-up in two centers. Epidermal nevi included verrucous epidermal nevi, nevus sebaceous, Becker nevi, inflammatory linear verrucous epidermal nevi and smooth-muscle hamartoma. We conclude that ablative lasers can treat verrucous epidermal nevi with good long-term esthetic results, but they have limited long-term efficacy for nevus sebaceous. Q-switched lasers failed to improve Becker nevi.

Laser induced smoke is a potential health hazard from laser procedures. During laser procedures, the thermal destruction of tissue creates a smoke byproduct. Research studies have confirmed that this smoke plume possibly contains toxic gases and vapors such as benzene, hydrogen cyanide, and formaldehyde, bioaerosols, dead and live cellular material and viruses. Methods of control of laser induced smoke are evaluated in this part.

Chapter 6 describes the effect of smoke evacuators on ultrafine particle concentrations during LHR.We aimed to assess the effect of different laser devices and different smoke evacuators on the ultrafine particle concentrations in the room during LHR. Ultrafine particle concentrations were measured during LHR for two different alexandrite lasers, with and without an external smoke evacuator. Moreover, we assessed a device for LHR with a smoke evacuator integrated into the handpiece. Both external and integrated smoke evacuators were effective with a 3.7-7-fold decrease in maximal ultrafine particle count. Similarly, maximal particle concentrations remained low with both smoke evacuators.

Chapter 7 focuses on current perceptions of health hazards of laser-induced smoke and smoke management among members of the European Society for Lasers and and Energy Based Devices (ESLD). The survey was distributed among 109 laser physicians from 40 countries. The study showed that the majority of physicians were aware of potential hazards of laser-induced smoke but also indicated a desire for better protective measures. A smoke evacuation system was frequently used with ablative - and fractional ablative lasers but rarely with non-ablative or hair reduction lasers. In conclusion, while there is awareness of the hazards of laser-induced smoke among physicians, implementation of regulations on safety measures is hampered by the lack of information, accessibility of high filtration masks, discomfort, excessive noise, financial issues, and high room temperatures.

Conclusion

There are numerous potential clinical uncommon indications for laser therapy, although quality of research for these disorders is relatively low. The development of a registry for international standardized documentation of laser therapy and settings used for different and uncommon indications could improve the overall quality of evidence. We assume that a generic outcome set will harmonize data collection. The standardization will make comparisons and meta- analyses between available laser devices possible and minimize over- and undertreatment in future. Furthermore, we also emphasize the importance of such a registry as this will lead to a greater understanding of the effectiveness and safety of laser treatments. Important next steps are consensus on outcome measurement instruments for the LEAD registry and establishment of implementation of regulations on safety measures.

Nederlandse Samenvatting

Laser treatments for skin diseases- Towards an international registry

Dit proefschrift bestaat uit twee delen. Het eerste deel behandelt de ontwikkeling van de Generic Core Outcome Set (GOS) voor het internationale Laser trEAtments in Dermatology (LEAD) register.

Het tweede deel beschrijft de effectiviteit van lasers voor epidermale naevi op lange termijn. Daarnaast worden verschillende aspecten van veiligheid besproken, variërend van het evalueren van laser-geïnduceerde rook tijdens laser ontharingsbehandelingen, tot de perceptie en het gebruik van veiligheidsmaatregelen door artsen.

Deel I: Ontwikkeling van de Generic Core Outcome Set (GOS) voor het internationale Laser trEAtments in Dermatology (LEAD) register

De snelle ontwikkeling van lasertechnologie in het afgelopen decennium heeft geleid tot de introductie van veel nieuwe indicaties voor laser behandelingen. Lasertherapie is een onmisbare therapeutische modaliteit geworden in de dermatologie. Dit komt tot uiting in het aantal artikelen waarin specifieke indicaties worden beschreven die vaak onder de zeldzame ziekten in de dermatologie behoren.

Er zijn echter beperkte gegevens over de rol van laserbehandelingen binnen het gehele spectrum van huidziekten. Over de effectiviteit van lasertherapie bij zeldzame ziekten is voornamelijk weinig informatie. Momenteel meten individuele onderzoekers uitkomsten die ze geschikt achten voor laser studies. Bij het samenvatten zien we dat er veel heterogeniteit is in de laser studies. Met het gebruik van diverse uitkomsten is het lastig om laserbehandelingen te vergelijken en te combineren.

Een internationaal register kan helpen om laserbehandelingen in de loop van de tijd te evalueren. Een standaardisatie van uitkomstmeting in deze studie is hiervoor essentieel.

Een Core Outcome Set (COS) is gedefinieerd als een minimale set van uitkomstmaten die ingezet kan worden in alle klinische onderzoeken naar een bepaalde ziekte of aandoening. De COS heeft het potentieel om de resultaten van onderzoek naar laserbehandelingen vergelijkbaar, analyseerbaar en relevant te maken.

Het is belangrijk dat, net als bij de COS voor klinische trials, een COS wordt ontwikkeld voor het verzamelen van data in de dagelijkse praktijk voor een register. In de dermatologie zijn er al verschillende COS ontwikkeld voor specifieke aandoeningen. Aangezien een grote verscheidenheid aan zeldzame dermatologische aandoeningen

met lasers wordt behandeld, was een logische volgende stap om een algemeen geldige generieke uitkomst set ('Generic Outcome Set' afgekort: GOS) te ontwikkelen voor het internationale register van Laser trEAtments in Dermatology (LEAD).

Een gedetailleerd protocol in **hoofdstuk 2** beschrijft het ontwikkelingsproces van de GOS die uit twee fasen bestaat:

1) een literatuuronderzoek om te bepalen welke uitkomsten vaak worden gebruikt in onderzoek naar laserbehandelingen voor een breed scala aan medische indicaties.
2) een consensus onderzoek om overeenstemming te bereiken over een generieke set van uitkomsten voor het LEAD-register volgens de Delphi-methodologie.

In **hoofdstuk 3**, als de eerste stap in de ontwikkeling van een generieke uitkomst set voor het LEAD-register, hebben we een systematische review uitgevoerd om uitkomsten, uitkomst meetinstrumenten, methoden en definities te identificeren aan de hand van recent gepubliceerde literatuur over laserbehandelingen voor verschillende huidaandoeningen. Twee onderzoekers bekeken hierbij onafhankelijk 150 onderzoeken, waaronder alle soorten onderzoeken met laserbehandelingen voor niet-cosmetische huidaandoeningen. Er werden 105 uitkomsten geïdentificeerd en gecategoriseerd in acht domeinen die worden aanbevolen door het zogenaamde COMET-framework: uiterlijk vertoon van de huidaandoening, langetermijneffecten, door arts en patiënt gerapporteerde symptomen, tevredenheid, kwaliteit van leven, impact van ziekte/aandoening op dagelijks activiteiten en bijwerkingen.

Heterogeniteit in uitkomst rapportage (bijv. categorieën en uitkomst meetinstrumenten) was aanwezig en definities werden onvoldoende gerapporteerd. De resultaten van deze review werden gebruikt in de volgende stap, de Delphi-consensus, om consensus te bereiken tussen belanghebbenden over de uitkomst domeinen die in het LEAD-registratie moeten worden geïmplementeerd.

Hoofdstuk 4 betreft de internationale e-Delphi-consensus studie. In 3 stemrondes werd besloten welke generieke uitkomst subdomeinen volgens artsen en patiënten het belangrijkst zijn voor het LEAD-register. In totaal werden 25 generieke uitkomsten gepresenteerd aan de deelnemers. In fase drie werd een online consensus meeting gehouden met 16 experts en 16 patiënten om consensus te bereiken over de uiteindelijke generieke uitkomsten (tabel 1), waarvan uiteindelijk negen generieke uitkomsten werden uitgekozen voor het LEAD-register: Uiterlijke vertoning van de huidziekte beoordeeld door arts, uiterlijke vertoning van de huidziekte beoordeeld door patiënten, textuur van het oppervlak, kleur, aangetaste oppervlakte (grootte), algehele kwaliteit van leven, impact van ziekte/aandoening op dagelijks fysieke activiteiten van het dagelijks leven, tevredenheid van de patiënt met het resultaat, patiënttevredenheid over de behandeling, lokale bijwerkingen (>6 maanden) en aantal behandeling sessies. Dit resulteerde in de

eerste internationale GDS voor een registratie over laserbehandelingen op basis van een internationale Delphi-studie.

Tabel 1. Definitieve GDS voor het LEAD-register

Core area	Generic Outcome Domain	Generic outcome Subdomain **first level**	Generic outcome Subdomain **second level**
Physical/ clinical	*Symptomen/signs door arts beoordeeld*	Uiterlijke vertoning van huidziekte beoordeeld door arts	Textuur oppervlakte Kleur Aangetast oppervlakte (grootte)
	Symptomen/ signs door patient beoordeeld	Uiterlijke vertoning van huidziekte beoordeeld door patient	
Life impact	*Kwaliteit van leven*	Algehele Kwaliteit van leven	Impact van ziekte/ aandoening op dagelijks fysiek activiteiten
	Satisfaction	Tevredenheid van patient met resultaat	Tevredenheid van patient met de behandeling
	Bijwerkingen	Lokale bijwerkingen (6 maanden)	
	Levering van de zorg	Aantal behandeling sessies.	

Deel II: Laserbehandelingen en veiligheid in de klinische praktijk

In **hoofdstuk 5** presenteren we de resultaten van een retrospectieve, cohortstudie, met alle patiënten die werden behandeld met, meestal ablatieve lasers voor een epidermale naevus, met een follow-up van meer dan een jaar in twee centra. Epidermale naevi bestaan uit verruceuze epidermale naevi, naevus sebaceous, Becker naevi, inflammatoire lineare verruceuze epidermale naevi and smooth-muscle hamartoma. We concluderen dat ablatieve lasers verruceuze epidermale naevi kunnen behandelen met goede esthetische resultaten op lange termijn. Voor nevus sebaceous is er een beperkte effectiviteit op lange termijn. Q-switched lasers konden Becker naevi niet verbeteren.

Tijdens laserprocedures ontstaat er door de thermische destructie van weefsel rook als een bijproduct. Door laser veroorzaakte rook tijdens laser procedures is een potentieel gevaar voor de gezondheid. Studies hebben bevestigd dat deze rook, zogenaamd ultrafijn stof, mogelijk giftige gassen en dampen bevat zoals benzeen, waterstofcyanide en formaldehyde, bioaerosolen, levend celmateriaal en virussen. In dit deel worden veiligheids methoden voor deze rook geëvalueerd.

Hoofdstuk 6 beschrijft het effect van rookafzuigsystemen op ultrafijnstof concentraties tijdens Laser Hair Removal (LHR). We beoordelen het effect van verschillende laserapparaten en verschillende rookafvoersystemen op de ultrafijnstof

concentraties in de kamer tijdens LHR procedures. Ultrafijnstof Concentraties werden gemeten tijdens LHR voor twee verschillende alexandriet lasers, met en zonder externe rookafzuiging. Bovendien hebben we een apparaat voor LHR beoordeeld met een in het handstuk geïntegreerde rookafzuiging. Zowel de externe als de geïntegreerde rookafzuiging waren effectief met een 3,7-7-voudige afname van het maximale aantal ultrafijne deeltjes. Evenzo bleven de maximale deeltjesconcentraties laag bij beide rookafzuigers.

Hoofdstuk 7 richt zich op de huidige percepties van gezondheidsrisico's van door laser veroorzaakte rook en beschermende maatregelen onder leden van de European Society for Lasers and and Energy Based Devices (ESLD). De enquête werd beantwoord door 109 artsen die met lasers werken, uit 40 landen. De studie toonde aan dat de meerderheid van de artsen zich bewust was van de mogelijke gevaren van laser-geïnduceerde rook, maar ook de wens aangaf voor betere beschermende maatregelen. Een rookafvoersysteem werd vaak gebruikt bij ablatieve - en fractionele ablatieve lasers, maar zelden bij niet-ablatieve of haarreductielasers. Concluderend, hoewel artsen zich bewust zijn van de gevaren van door laser veroorzaakte rook, wordt de implementatie van regelgeving over veiligheidsmaatregelen belemmerd door het gebrek aan informatie, de toegankelijkheid van maskers met hoge filtering, ongemak tijdens laser procedures, overmatig lawaai, kosten van apparatuur en hoge kamertemperatuur.

Conclusie

Er zijn tal van potentiële klinische zeldzame indicaties voor lasertherapie, hoewel de algehele kwaliteit van laseronderzoek voor deze ziekten relatief laag is. De ontwikkeling van een register voor internationaal gestandaardiseerde documentatie van lasertherapie en instellingen die worden gebruikt voor verschillende en ongebruikelijke indicaties zou de algehele kwaliteit van het bewijs kunnen verbeteren. We stellen dat een generieke uitkomstmaten set hierbij kan helpen. De standaardisatie maakt vergelijkingen en meta-analyses tussen beschikbare laserapparaten mogelijk en minimaliseert over- en onder behandeling in de toekomst. Verder benadrukken we ook het belang van een dergelijke registratie omdat dit zal leiden tot een beter begrip van de effectiviteit en veiligheid van laserbehandelingen. Belangrijke vervolgstappen zijn consensus over uitkomst meetinstrumenten voor de LEAD-registratie en het vaststellen van de implementatie van regelgeving over beschermingsmaatregelen tijdens laserprocedures.

ADDENDUM

Abbreviations

List of contributing authors

List of publications

PhD Portfolio

Dankwoord

Curriculum vitae

Abbreviations

AUMC	Amsterdam University Medical Centre
BN	Becker nevus
CO2 laser	Carbon dioxide laser
COMET	Core Outcome Measures in Effectiveness Trials
COS	Core outcome set
COSMIN	COnsensus-based Standards for the selection of health Measurement Instruments
CSG-COUSIN	Cochrane Skin Group - Core Outcome Set Initiative
DLQI	Dermatology Life Quality Index
Er:YAG laser	Erbium yttrium aluminum garnet laser
EN	Epidermal Nevus
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluations
GOS	Generic Outcome Set
GDS	Generic Outcome Domain Set
HRQoL	Health-related quality of life
IPL	Intense pulsed light
LASER	Light amplification by stimulated emission of radiation
LEAD	Laser trEAtments in Dermatology
LHR	Laser Hair Removal
LT-PGA	Long-term physician global assessment
Nd:YAG laser	Neodymium yttrium aluminum garnet laser
NS	Nevus Sebaceous
PGA	Patient Global Assessment
PIH	Postinflammatory hyperpigmentation
RAVEN	Rounded and velvety epidermal nevus
RCT	Randomized Controlled Trial
RR	Response Rate
SR	Systematic review
UFP	Ultrafine Particles
VAS	Visual analogue scale
VEN	Verrucous Epidermal Nevus
WHO	World Health Organization
WMO	Medical Research Involving Human Subjects Act

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List of publications

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Alkhalifah, A., Fransen, F., Le Duff, F., Lacour, J. P., Wolkerstorfer, A., & Passeron, T. (2020). Laser treatment of epidermal nevi: A multicenter retrospective study with long-term follow-up. *Journal of the American Academy of Dermatology*, *83*(6), 1606–1615.

Fransen, F., Spuls, P., Alam, M., Badawi, A., Boixeda, P., Haedersdal, M., Hamzavi, I., Hedelund, L., Kelly, K. M., Kono, T., Laubach, H. J., Manuskiatti, W., Marini, L., Nouri, K., Paasch, U., Passeron, T., Prinsen, C., Verner, I., & Wolkerstorfer, A. (2020). Generic outcome set for the international registry on Laser trEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on *what* to measure. *BMJ open*, *10*(6), e038145.

J A de Boer, A., Fransen, F., R Bloemen, P., A Meesters, A., A de Rie, M., & Wolkerstorfer, A. (2022). Ultrafine particle concentrations during laser hair removal: Effectiveness of smoke evacuators. *Lasers in surgery and medicine*, *54*(2), 217–223.

Fransen, F., Hiel, M.A.J., Al-Niami, F., Headersdal, M., Laubach, HJ., Snauwaert, JE., Wolkerstorfer, A. (2022). Laser-induced smoke in dermatologic practice: A survey to explore hazard perceptions, safety measures and unmet needs. *Journal of Laser in Medical Sciences (JLMS)*

Fransen, F., Spuls, P., Alam, M., Alkhalifa, A., Badawi, A., Boixeda, P., Haedersdal, M., Hamzavi, I., Hedelund, L., Kelly, K. M., Kono, T., Laubach, H. J., Manuskiatti, W., Marini, L., Nouri, K., Paasch, U., Passeron, Revelo, Heidi. C., Verner, I., & Wolkerstorfer. A. (2022) A Generic Domain Set for a registry on laser treatments in dermatology: a Delphi process and consensus meeting. *BJD. (submitted)*

Other

Fransen, F., Martens, H., Nagtzaam, I., & Heeneman, S. (2018). Use of e-learning in clinical clerkships: effects on acquisition of dermatological knowledge and learning processes. *International Journal of Medical Education,12:169-178.*

PhD Portfolio

AMC Graduate School for Medical Sciences
Name PhD student: F.Fransen
PhD period: February 2018 – September 2022
Promotor: Prof. M.A. de Rie
Co-promotor: Dr. A. Wolkerstorfer
Institution: Department of Dermatology, Amsterdam University Medical Center

PhD Training	Year	Workload hours/ ECTS
General courses, seminars, workshops, masterclasses		
European Academy of Dermatology and Venereology, Paris, France	2018	0.3
Weekly scientific meeting of department	2018-2019	1.8
PhD Talents course, Amsterdam University Medical Center		
Communication with patients, Amsterdam University Medical Center		
ESLD Teaching Course: Hands On Laser & EBD, Amsterdam	2018-2019	0.6
Fundamentals of Lasers for Dermatological Application Course, Denver, U.S.A	2018	0.5
Laser Safety in the Practice Environment, Denver, U.S.A	2019	0.5
	2019	0.5
	2019	0.5
(Inter)national oral presentations		
27th congress of European Academy of Dermatology and Venereology (EADV), Paris, France. F.Fransen, A. Wolkerstorfer. Oral Presentation closed meeting: "the LEAD registry"	2018	0.5
39th Annual Conference of the American Society for Laser Medicine and Surgery (ASLMS), Denver, U.S.A."A systematic review of outcome reporting in laser treatments for dermatological diseases"	2019	0.5
Journées Parisiennes du Laser 2019, Paris, France." Initiative of International Laser Registry"	2019	0.7
28th congress of European Academy of Dermatology and Venereology (EADV), Madrid, Spain. .F.Fransen, A. Wolkerstorfer, LEAD Registry steering committee. " First steps towards the international Laser Registry"	2019	0.5

PhD Training	Year	Workload hours/ ECTS
(Inter)national conferences		
- Annual Cochrane Skin Group Meeting 2018, Amsterdam, The Netherlands	2018	0.3
- Euro Laser conference, Rotterdam, The Netherlands	2018	1.25
- 27th congress of European Academy of Dermatology and Venereology, Paris, France	2018 2019	1.25
- 39th Annual Conference of the American Society for Laser Medicine and Surgery (ASLMS), Denver, U.S.A.	2019	1.25
- Journées Parisiennes du Laser 2019, Paris, France	2019	1.25
- 28th congress of European Academy of Dermatology and Venereology, Madrid, Spain	2019	0.7
II. Teaching		
Supervising		
Internship Dewi Rijnenberg (master student) topic: laser treatments for Hidradenitis suppurativa)	2019	1.5
Internship Anne de Boer (master student) topic: laser treatment for acne and ultrafine particles during laser hair removal treatments	2019	0.5
Extra scientific internship Marjolein Hiel (master student): survey on safety measures during laser treatments	2020	0.5
III. Parameters of Esteem		
Grants		
ASLMS Educational Grant Associated with the abstract of "A systematic review of outcome reporting in laser treatments for dermatological diseases"	2019	

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Lieve doctoren uit ons stadsie, Utrecht. Ik heb altijd gezworen na jullie PhD geen PhD te doen. Dat is alleen niet gelukt.

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Curriculum vitae

Frederike Fransen was born in Edam on December 21, 1990. She grew up in this place with her elder brother Wouter and parents Tom and Dineke. In 2009, she obtained her Gymnasium degree at OSG West-Friesland and she enrolled in the Liberal Arts and Science program of University College Utrecht. During her bachelor studies she followed a wide range of interdisciplinary courses and found her interests in life sciences, health psychology and sociology. She enjoyed her participation in the dance committee and explored the student campus life in Canada during an exchange program at Queen's University, Ontario. A time that also provided the opportunity to do what she loves most: surf and hike in the surrounding nature.

After obtaining her Bachelor Science degree with honors and she left Europe for an in-hospital program focused on tropical diseases in Sudan, Africa. She witnessed daily practice with fascinating diseases and these experiences guided her choice to start medical school in Maastricht. As part of her 4-year selective master Physician-Clinical-Investigator master, she worked on research projects concerning e-Health in collaboration with University of Mekelle, Ethiopia in Africa. For her final rotations she was stationed in the MUMC+ hospital of Maastricht with a research internship at the department of Dermatology.

In 2018, she started as a PhD-candidate under the supervision of Dr. A. Wolkerstorfer at the department of Dermatology at AUMC, focusing on the development of a generic outcome set for a laser registry in dermatology, which led to the formation of this thesis. Besides her PhD, she worked as a resident not in training at the Ceulen Klinieken. In 2022, she started training and working in injectable treatments at Cosmetique-Totale. As aesthetic medicine is a fast growing and exciting field, she appreciates the opportunity to be part of its development.