VASPVT
Valstybinė akreditavimo
sveikatos priežiūros veiklai tarnyba
prie Sveikatos apsaugos ministerijos

SVEIKATOS TECHNOLOGIJOS VERTINIMAS:
INTRASTROMINIAI RAGENOS IMPLANTAI EKTAZINIŲ RAGENOS PAKITIMŲ KOREKCIJAI

HEALTH TECHNOLOGY ASSESSMENT:
INTRASTROMAL CORNEAL IMPLANTS FOR ECTATIC CORNEAL DISORDERS

2016
VILNIUS

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TABLE OF CONTENTS

ABBREVIATIONS

% – percent;
BCVA – best-corrected visual acuity;
CCT – computerised corneal topography;
CE – Communauté Européenne;
CISIS – corneal intrastromal implantation system;
CXL – corneal cross-linking;
DALK – deep anterior lamellar keratoplasty;
DNA – deoxyribonucleic acid;
DRG – Diagnosis Related Groups system.
e.g. – for example;
etc. – et cetera;
FDA – Food and Drug Administration;
HLA – human leukocyte antigen;
HUD – Humanitarian Use Device;
ICD-10-AM – International Classification of Diseases, 10th Revision, Australian Modification;
ICRS – intracorneal/ intrastromal ring segments;
LASIK – laser-assisted in situ keratomileusis;
LBI-HTA – Ludwig Boltzmann Institute for Health Technology Assessment;
NICE – National Institute for Health and Care Excellence;
PK – penetrating keratoplasty;
PRK – photorefractive keratectomy;
RSB – residual stromal bed;
TE-CXL – transepitheliail corneal cross-linking;
UCVA – uncorrected visual acuity;
UVA – ultraviolet-A light.

SANTRAUKA

Sveikatos technologijos vertinimo metodika

Šis sveikatos priežiūros technologijos vertinimas yra Austrijos Liudviko Boltzmano instituto sveikatos technologijų vertinimui (angl. *Ludwig Boltzmann Institute-Health Technology Assessment, Austria*) atlikto vertinimo „Intrastrominiai ragenos implantai ektazinių ragenos pakitimų korekcijai“ (angl. *„Intrastromal corneal implants for ectatic corneal disorders”*) atnaujinimas ir adaptavimas Lietuvos kontekstui pagal EUnetHTA metodikas. Europos Komisija inicijuoja ir remia EUnetHTA atliktų sveikatos priežiūros technologijų vertinimų naudojimą ir adaptavimą nacionaliniams Europos šalių poreikiams.

Pirminis šaltinis, kurio pagalba buvo atrinkti pagrindiniai vertinimo elementai – Sveikatos technologijų vertinimo šerdinis modelis medicininių ir chirurginių intervencijų vertinimui, versija 3.0 (angl. *‘HTA Core Model® for Medical and Surgical Interventions (version 3.0’*). Be to, kiti EUnetHTA šerdinio modelio dokumentai buvo peržiūrėti ir, esant poreikiui, papildomi vertinimo elementai įtraukti.

2016-ųjų metų birželio mėn. vykdyta sisteminė literatūros paieška buvo tikslinama naudojant duomenų filtrą – publikacijos išspausdintos laikotarpyje nuo 2014-ųjų metų gruodžio mėn. 30 d. iki 2016-ųjų metų birželio mėn. 21 d., imtinai. Dalis informacijos buvo atnaujinta ir panaudota remiantis Austrijos Liudviko Boltzmano instituto sveikatos technologijų vertinimui (LBI-HTA, Austrija) atliktu sveikatos technologijų vertinimu, įvardinamu kaip sprendimų paramos dokumentas Nr. 85 „Intrastromal corneal implants for ectatic corneal disorders”.

Intrastrominių ragenos implantų vertinimo analizė atlikta remiantis mokslinės literatūros šaltiniais, esančiais:

- The Cochrane Library duomenų bazėje;
- PubMed (Medline) duomenų bazėje;
- CRD duomenų bazėje;
- Gamintojų internetiniuose puslapiuose, kurių ieškota rankiniu būdu viešai prieinamoje erdvėje (internete).

Straipsniai, skirti „Saugumo“ ir „Klinikinio efektyvumo“ skyrių adaptavimui, buvo atrinkti VASPVT (Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba prie Sveikatos apsaugos ministerijos, Lietuva) Medicinos technologijų skyriaus specialistų. Papildomi moksliniai straipsniai buvo įtraukti arba atmesti vadovaujantis PICO lentele, kuri pateikta santraukoje.

Mokslinių straipsnių įtraukimo ir atmetimo procesą vykdė du tyrėjai. Jei ta pati informacija dubliavosi keliuose straipsniuose, į vertinimą įtraukti tik tie, kuriuose rezultatai pateikti išsamiausiai arba straipsniai buvo naujausi. Visais atvejais, tiek atmetant, tiek įtraukiant tyrimus į vertinimą buvo siekiama bendro sutarimo.

Vertinime naudojamų prospektyvinių nelyginamųjų tyrimų kokybė buvo tikrinta specialiu, nekontroliuojamiems tyrimams skirtu, Sveikatos Ekonomikos instituto kontrolės klausimynu (angl. *The IHE checklist*), kurio rezultatus galima rasti Austrijos LBI-HTA instituto sveikatos technologijų vertinime, įvardintame kaip sprendimų paramos dokumentas Nr. 85 „Intrastromal corneal implants for ectatic corneal disorders”. Randomizuoto kontroliuojamo tyrimo kokybė tikrinta specialiu „The Cochrane risk of bias“ kontrolės klausimynu (žr. Priedas 4). Vertinime naudojamų sisteminių literatūros apžvalgų kokybė buvo patikrinta specialiu, sisteminėms literatūros apžvalgoms skirtu, „AMSTAR“ kontrolės klausimynu (žr. Priedas 4). Visus klausimynus individualiai pildė du specialistai.

Kadangi buvo rastas tik 1 randomizuotas kontroliuojamas tyrimas, palyginti skirtingų produktų rūšių nepavyko. Be to, kitų įtrauktų tyrimų kokybė neleido atlikti palyginamosios analizės. LBI-HTA agentūros specialistai „Saugumo“ ir „Klinikinio efektyvumo“ skyriuose pateiktų duomenų kokybę įvertino remiantis tarptautinėmis Rekomendacijų lygių Vertinimo ir Nustatymo Grupės rekomendacijomis (angl. *The Grading of Recommendations Assessment, Development and Evaluation, GRADE*). Penkių vienpusių į vertinimą įtrauktų tyrimų pagrindinių charakteristikų lentelės yra Austrijos LBI-HTA instituto sveikatos technologijų vertinime, kuris įvardinamas kaip sprendimų paramos dokumentas Nr. 85 „Intrastromal corneal implants for ectatic corneal disorders”.

Atsakant į „Sveikatos problema ir dabartinis technologijos naudojimas“ bei „Techninės charakteristikos“ skyrių klausimus, į vertinimą įtrauktiems tyrimams jokie apribojimai netaikyti, informacijos ieškota rankiniu būdu viešai prieinamoje erdvėje (internete).

Didžioji dalis vertinime pateiktų klausimų buvo atsakyta tekstiniu formatu. Atrinktų tyrimų bei juose analizuojamų populiacijų pagrindinės charakteristikos ir rezultatai, susiję su klinikiniu efektyvumu bei saugumu, pateikti lentelėse (žr. Priedas 3). Kadangi trūksta palyginamųjų grupių ir duomenys yra heterogeniški, atlikta analizė yra ne kiekybinė, bet kokybinė.

PICO lentelė	
Populiacija	Pacientai, kuriems nustatyta: • Keratokonusas (pagal TLK-10-AM: H18.6) ✓ kai negali naudoti akinių ar kontaktinių lęšių (dėl netoleravimo) arba ✓ kai akiniai ar kontaktiniai lęšiai nepakankamai pagerina regėjimo aštrumą; • Jatrogeninė ragenos ektazija, atsiradusi po LASIK[1] operacijos (TLK-10-AM: H18.7[2]). *MeSH-terms: C11 Eye Diseases, C11.204 Corneal Diseases, C11.204.627 Keratoconus*
Intervencija	Intrarageniniai žiedų segmentai (ICRS), arba intrarageniniai žiedai, arba intrastrominiai ragenos žiedai, arba intrastrominiai ragenos implantai. Produktų pavadinimai: Ferrara RingTM (Ferrara OphthalmicsTM); Intacs® (Addition TechnologyTM); Keraring (Mediphacos); MyoRing® (DIOPTEX); [Bisantis Segments (Optikon), tikriausiai nebenaudojamas]. *MeSH-terms: E07.695 Prostheses and Implants, E07.695.225 Eye, Artificial.*
Alternatyvos	• Ragenos transplantacija; • Jokios intervencijos.[3]
Rezultatai	
Efektyvumas	• Lovadienių skaičius (arba laikas iki darbo atnaujinimo); • Gyvenimo kokybė (susijusi su sveikata arba regėjimu); • Pakartotinių operacijų dažnis; • Pacientų pasitenkinimas; • Regėjimo aštrumo pokytis.

[1] Lazerinė in situ ragenos korekcija.

[2] LBI-HTA specialistai iš TLK-10-AM pasirinko kodą Q13.4, kuris jatrogeninę ragenos ektaziją, atsiradusią po LASIK operacijos, apibūdina kaip įgimtą būklę. Vis dėlto, VASPVT specialistai šiai būklei apibrėžti pasirinko kitą, H18.7 kodą (Kitos ragenos deformacijos).

[3] Jokios intervencijos neatlikimas buvo laikomas kaip alternatyva tuo atveju, jei nebus tinkamų kontroliuojamųjų tyrimų.

Saugumas	• Nepageidaujami įvykiai (per- ir po- operaciniai).
Tyrimų tipas	
Efektyvumas	• Randomizuoti kontroliuojami tyrimai; • Prospektyviniai nerandomizuoti kontroliuojamieji tyrimai; • Prospektyviniai vienpusiai tyrimai (kai įtraukta 50 ir daugiau akių).
Saugumas	• Randomizuoti kontroliuojami tyrimai; • Prospektyviniai nerandomizuoti kontroliuojamieji tyrimai; • Prospektyviniai vienpusiai tyrimai (kai įtraukta 50 ir daugiau akių).
PICO klausimas: Ar intrastrominiai ragenos žiedai pacientams, kuriems nustatytas keratokonusas ir kai pacientai negali naudoti akinių ar kontaktinių lęšių dėl netoleravimo arba kai akiniai ar kontaktiniai lęšiai nepakankamai pagerina regėjimo aštrumą arba kuriems nustatyta jatrogeninė ragenos ektazija, atsiradusi po LASIK operacijos, yra efektyvesnis ir saugesnis gydymo būdas atsižvelgiant į regėjimo aštrumo pokytį, lovadienių skaičių, gyvenimo kokybę, pakartotinių operacijų dažnį ir nepageidaujamus įvykius lyginant su ragenos transplantacija ar jokio gydymo netaikymu?	

Tikslinė būklė

Keratokonusas – neuždegiminė, dažniausiai abipusė, ragenos ektazija, kuriai būdingas progresuojantis ragenos išlinkimas ir stromos plonėjimas, galintis pasireikšti (arba ne) nereguliariu astigmatizmu bei mažėjančiu regėjimo aštrumu. Ragenos paviršiuje gali susidaryti akivaizdus kūgio formos išsikišimas. *Jatrogeninė ragenos ektazija, atsiradusi po LASIK operacijos*, yra reta, bet rimta LASIK (refrakcinės) operacijos komplikacija. Ši būklė panaši į keratokonusą, kai ragena pradeda gaubtis praėjus kuriam laikui po LASIK operacijos. **(A0002)**

Keratokonuso patofiziologija nėra gerai išaiškinta. Manoma, kad genetiniai veiksniai yra daugiausiai lemiantys ir laikomi esminiais keratokonuso etiologijai ir progresavimui. Tikėtina ragenos ektazijos priežastis yra genetinių veiksnių ir ragenos anatominės destabilizacijos (refrakcinės operacijos metu) derinys. Antrinė ektazija gali būti sukelta vien tik mechaninio proceso metu ir gali būti vienpusė. Nors ektazija gali atsirasti po įvairių refrakcinių operacijų, tačiau dažniausiai pasitaiko po LASIK operacijos. **(A0003)**

Keratokonusas paprastai prasideda paauglystėje/ jaunystėje (amžiaus mediana – 25 m.) ir progresuoja iki 30-tųjų – 40-tųjų gyvenimo metų. Keratokonusą lydi regėjimo aštrumo sumažėjimas, ragenos plonėjimas, šviesos baimė, akių sudirgimas. Ragenos ektazija yra viena iš pažeidžiamiausių komplikacijų po LASIK operacijos. Ektaziniai pokyčiai gali pasireikšti labai anksti (po savaitės) arba labai vėlai (po kelerių metų) po atliktos LASIK operacijos. LASIK operacija suplonina ir susilpnina rageną, o tai gali lemti progresuojantį ragenos išsigaubimą ir su tuo susijusį regėjimo blogėjimą. **(A0004; A0005)**

Tikslinė populiacija

Tikslinė populiacija yra pacientai, kuriems diagnozuotas keratokonusas (dažniausiai 1–3 stadijos) arba po LASIK refrakcinės operacijos atsiradusi ragenos ektazija, ir kurie netoleruoja kontaktinių lęšių (pacientai, kuriems diagnozuotas keratokonusas) bei neturi randų centrinėje ragenos dalyje, bet yra pakankamas ragenos storis būsimo pjūvio vietoje. **(A0007)**

Keratokonuso sergamumas per metus siekia 2 atv./ 100,000 žm., o ligotumas svyruoja nuo <10 iki >50 atv./ 100,000 žm. Tikrasis ragenos ektazijos, atsiradusios po LASIK operacijos, sergamumas nėra žinomas, tačiau manoma, kad ši būklė išsivysto mažiau nei 1% pacientų, patyrusių LASIK operaciją. Lietuvoje 2015 m. iš viso atlikta 16,509 operacinės intervencijos, susijusios su ragena, rainele ir lęšiuku. **(A0005; A0006; A0011)**

Pasekmės visuomenei neatrodo didelės dėl abiejų indikacijų mažo sergamumo, tačiau pacientui pasekmės yra reikšmingos, galinčios paveikti gyvenimo kokybę bei nulemti negalią. **(A0005; A0006)**

Šiuolaikinis būklės valdymas

Kompiuterinė ragenos topografija, naudojanti išlinkimo analizę, tomografija, naudojanti pakilimo analizę, yra jautriausi ir plačiausiai prieinami ankstyvųjų bei vidutinių stadijų keratokonuso ir ragenos ektazijos, atsiradusios po LASIK operacijos, aptikimo metodai. Deja, bet nėra universalių diagnostikos kriterijų ankstyvosioms šių būklių formoms diagnozuoti. Pažengusios stadijos gali būti diagnozuojamos biomikroskopijos (plyšinės lempos) metodu. **(A0024)**

Šiuo metu nėra jokių vaistų, skirtų keratokonuso gydymui ar prevencijai. Vis dėlto, pacientai gali sulėtinti ligos progresavimą netrindami akių. Dėl ankstyvojo keratokonuso (lengvo ar vidutinio sunkumo) atsiradęs regėjimo sutrikimas gali būti koreguojamas minkštais kontaktiniais lęšiais, akiniais arba intrarageninio žiedo/ žiedo segmento implantacija. Ligai progresuojant vis sunkiau atkurti regėjimo aštrumą, tad gali prireikti pasluoksninės arba kiaurinės keratoplastikos. **(A0025)**

Norint atkurti gerą regėjimą didėjant astigmatizmo žalai, gali prireikti standžių, orai pralaidžių kontaktinių lęšių. Kai kurie pacientai dėl komforto ir geresnio regėjimo pageidauja naudoti ir minkštąjį, ir standųjį kontaktinius lęšius. Pacientams, kuriems liga gerokai progresavusi (ne mažiau nei 2 stadija), gali būti sudėtinga ir nepatogu naudoti kontaktinius lęšius dėl ragenos išgaubtumo. Kontaktinių lęšių netoleravimas šioje ligos stadijoje yra dažna indikacija ragenos transplantacijai. **(A0025)**

Ragenos ektazijos, atsiradusios po LASIK operacijos, gydymo galimybės yra tokios pat kaip keratokonuso. **(A0025)**

Kompensavimas

Intrarageniniai implantai buvo sukurti trumparegystės (miopijos) gydymui; šiai indikacijai keli produktai gavo leidimą Europos rinkoje (CE ženklinimas). Vis dėlto, intrarageniniai implantai niekada nepasiekė trumparegystės gydymo komercinės sėkmės. Taip pat intrarageniniai implantai buvo pripažinti kaip terapinė alternatyva ektaziniams ragenos pakitimams, tokiems kaip keratokonusas ir ragenos ektazija, atsiradusi po LASIK operacijos, gydyti. **(A0020)**

Penkių gamintojų intrastrominiai ragenos implantai, skirti keratokonusui ir ragenos ektazijai, atsiradusiai po LASIK operacijos, yra prieinami rinkoje ir patvirtinti Communauté Européenne (CE) ženklinimu. JAV Maisto ir vaistų administracija yra patvirtinusi gamintojo Intacs® implantus, tačiau lengvata sveikatos technologijai buvo suteikta humanitariniais tikslais. **(A0020)**

Vis dėlto, intrastrominiai ragenos implantai, skirti keratokonusui ir ragenos ektazijai, atsiradusiai po LASIK operacijos, koreguoti, nėra įtraukti į kompensuojamųjų sąrašus Lietuvoje, tačiau implantų įterpimo operacija yra kompensuojama pagal DRG sistemą. **(A0021)**

Pagrindinės technologijos charakteristikos

Ragenos implantai yra nedideli žiedo segmentai arba pilnos formos žiedai, pagaminti iš sintetinių medžiagų (pvz., polimetilakrilato ar akrilatų polimerų). Jie implantuojami į ragenos stromą pacientams, kuriems diagnozuotas lengvos ar vidutinės sunkumo stadijos keratokonusas arba jatrogeninė ragenos ektazija, atsiradusi po LASIK operacijos, ir tokiu būdu ragenos paviršius tampa plokštesnis. Intrarageniniai žiedai ar jų segmentai implantuojami į tunelio pavidalo pjūvius, kurie sukuriami mechaniškai arba su femtosekundiniu lazeriu.

Yra 5 intrarageninių implantų rūšys. Vis dėlto, panašu, jog pirmosios kartos implantai Bisantis Segments (Optikon 2000 SpA ir Soleko SpA, Italija) yra nebegaminami, nes nepavyko rasti gamintojų internetinio puslapio (ieškota 2016-ųjų liepos mėn. 25 d.) Pagrindinės 4 intrarageninių implantų rūšys ir jų gamintojai:

- Ferrara Ring™ (AJL OPHTHALMIC S.A., Ispanija),
- Intacs® ir Intacs® SK (AJL OPHTHALMIC S.A., Ispanija),
- Keraring-Intrastromal corneal ring (Mediphacos, Brazilija),
- MyoRing® (DIOPTEX, Austrija). **(B0001)**

Pagrindinis skirtumas tarp šių gaminių yra implantų dizainas (pilnos formos žiedas ar tik žiedo segmentas). Tik MyoRing® implantai yra pilno žiedo formos, kiti – žiedo segmentai. Taip pat skiriasi ir implantų diametras, storis.

Intrarageniniai žiedų segmentų implantai nuo 1990-ųjų naudojami miopijai gydyti, o nuo 2004-ųjų – kitiems ektaziniams ragenos pakitimams koreguoti. Ši sveikatos technologija, kaip ir ragenos transplantacijos procedūra, yra visiškai sukurta ir ištobulinta. **(B0003)**

Pagrindinis intrarageninių žiedų segmentų implantacijos pranašumas prieš kitas chirurgines intervencijas (pvz. ragenos transplantaciją) – esant poreikiui, sąlyginai nesudėtingas implantų pašalinimas. Tai suteikia tolimesnę galimybę koreguoti problemą, vienus implantus pakeičiant kitais. Implantacija yra minimaliai invazinė procedūra, tai leidžia pacientams greitai grįžti į darbą ir užsiimti įprastine veikla, priešingai nei po ragenos transplantacijos. **(B0001; B0002)**

Paprastai intrarageninių žiedų segmentų implantaciją atlieka gydytojas oftalmologas-chirurgas, jam padeda du slaugytojai. Procedūra gali būti atliekama su vietine arba bendąja nejautra, tiek stacionare, tiek ambulatorinėmis sąlygomis. **(B0004)**

Dažniausiai ektaziniai ragenos pakitimai koreguojami specialiais kontaktiniais lęšiais (pirminėse keratokonuso stadijose), ligai progresuojant – atliekama ragenos transplantacija. Vis dėlto, kai kontaktiniai lęšiai netoleruojami, galima atlikti būtent intrarageninių žiedų segmentų implantaciją (ypač, kai nėra kitų akies patologijų). **(B0001)**

Ragenos sustiprinimas (angl. *corneal cross-linking*) yra dar viena sąlyginai nauja gydymo galimybė, kurios tikslas – sustabdyti ligos (keratokonuso) progresavimą. Procedūros metu naudojamas riboflavino (vitaminas B2) tirpalas ir ultravioletiniai-A (UVA) spinduliai; ši kombinacija veikia fotocheminės reakcijos principu, sukuriamos naujos cheminės jungtys ragenos audinyje. Ragena yra įsotinama riboflavinu, kuris susikaupia išilgai ragenos kolageno fibrilių. Apšvietus rageną UVA spinduliais, riboflavinas juos absorbuoja ir vykstant fotocheminei reakcijai bei laisvųjų radikalų susidarymui susiformuoja naujos jungtys ragenos stromoje tiek tarp kolageno fibrilių, tiek pačioje fibrilėje. Dėl šio proceso sutvirtėja ragenos audinys bei sumažėja centrinės ragenos dalies gaubtumas.

Kartais ragenos stiprinimo procedūra aktliekama kartu su kitomis intervencijomis (pvz., intrarageninių žiedų segmentų implantacija arba fotorefrakcine keratektomija. **(B0001)**

Vėlesnėse keratokonuso stadijose, kai yra susidarę randai regėjimo ašyje, intrarageninė implantacija ar kontaktiniai lęšiai dažniausiai nepadeda pagerinti regėjimo, todėl geriausia išeitis yra

ragenos transplantacija (keratoplastika), kiaurinė arba pasluoksninė, priklausomai nuo pažeistos ragenos randinio audinio dydžio. Pažeisti ragenos audiniai yra pakeičiami sveikais ragenos audiniais iš donoro. **(B0001)**

Investicijos ir prietaisai, reikalingi technologijos naudojimui

Norint atlikti intrarageninių žiedų segmentų implantacijos procedūrą, kaip ir atliekant ragenos transplantaciją, reikalinga sterili operacinė. **(B0008; B0009)**

Žiedai ar jų segmentai implantuojami į specialius tunelius ragenos stromoje, kurie sukuriami mechaniškai arba su femtosekundiniu lazeriu, taigi reikalingi tam tikri specialūs instrumentai (pvz., specialus kablys, pusiau automatinis siurbimo žiedas, specialus skalpelis ir kt.). **(B0008; B0009)**

Pacientų saugumas

Nebuvo rastas nė vienas tyrimas, kuriame tiesiogiai būtų lyginami intrarageniniai implantai su taikoma ragenos transplantacija arba su keratokonuso negydymu. **(C0008)**

Vis dėlto, buvo rastas 1 prospektyvinis randomizuotas tyrimas, kuriame palygintos 2 pacientų grupės: intervencijos grupės pacientams implantuoti intrarageninių žiedų segmentai (Keraring), kontrolinės grupės pacientams taip pat implantuoti intrarageninių žiedų segmentai (Keraring), tačiau po mėnesio jiems papildomai atlikta ragenos sustiprinimo procedūra. Vienam pacientui 1-oje akyje išsivystė implanto erozija ir implantas buvo „išstumtas“ iš akies. Deja, šis pacientas iš tyrimo buvo pašalintas, taip pat lieka neaišku, kurioje pacientų grupėje įvyko nepageidaujamas įvykis. **(C0008)**

Bendras nepageidaujamų atvejų dažnis po implantacijos procedūrų vienpusiuose tyrimuose įvyksta 7–16% akių. Implantacijos metu įvykstantys nepageidaujami įvykiai, tokie kaip sudėtingas specialaus tunelio ragenoje suformavimas ar priekinės stromos dalies perforacija, įvyksta 0–2% akių. Pooperaciniai nepageidaujami įvykiai įvyksta 2–23% gydytų akių, pvz., intrarageninio implanto išstūmimas ar pasislinkimas iš implantacijos vietos, infekcija ar ragenos perforacija. **(C0008)**

Nėra rasta tiesioginių įrodymų, kad būtų galima įvertinti kaip keičiasi nepageidaujamų įvykių dažnis ir sudėtingumas bėgant laikui ar esant tam tikroms aplinkybėms. Vis dėlto, panašu, jog kuo didesnis laiko tarpas praeina nuo implantacijos, nepageidaujamų įvykių dažnis nežymiai didėja. **(C0004)**

Taip pat nėra rasta tiesioginių įrodymų, jog vienos pacientų grupės yra pažeidžiamesnės už kitas. Negalima atsakyti ir į klausimą kaip nepageidaujamų įvykių dažnis priklauso nuo specialisto, atliekančio implantacijos procedūrą. Vis dėlto, reikia atkreipti dėmesį, jog visuose į vertinimą įtrauktuose tyrimuose buvo pažymėta, kad intrarageninių žiedų segmentų implantaciją atliko patyrę oftalmologai-chirurgai. **(C0005; C0007)**

Mirštamumas

Mirštamumas nėra svarbus rezultatas vertinant klinikinį intrarageninių implantų efektyvumą, nes nei būklės, nei intervencija nėra pavojingos gyvybei. **(D0001)**

Sergamumas

Regėjimo aštrumo pokytis per vieną ar daugiau Snellen‘o optotipų eilučių buvo aptariamas keturiuose vienpusiuose tyrimuose. Praėjus 12 mėn. po implantacijos, nekoreguotas regėjimo aštrumas (UCVA) pagerėjo 70–80% akių, o pablogėjo mažiau nei 10% akių; praėjus 24 mėn., pagerėjo 81% akių, o pablogėjo 4–12% gydytų akių. Panašiai kito ir geriausias koreguotas regėjimo aštrumas (BCVA) – praėjus 12 mėn., pagerėjo 60–85% akių, o pablogėjo 5% gydytų akių; praėjus 24 mėn., pagerėjo 68% akių, o pablogėjo 15% akių. **(D0005)**

Regėjimo aštrumo pokytis per dvi ar daugiau Snellen‘o optotipų eilučių buvo aptariamas trijuose vienpusiuose tyrimuose (viename tyrime UCVA, dviejuose – BCVA). Praėjus 6 mėn. po implantacijos, UCVA pagerėjo 79% akių, ir niekam nepablogėjo. BCVA, praėjus 6 mėn., pagerėjo 39-62% akių, o pablogėjo 6–12% gydytų akių; praėjus 12 mėn., pagerėjo 42% akių, o pablogėjo 8% gydytų akių. **(D0005)**

Regėjimo aštrumo pokytis buvo aptariamas ir randomizuotame kontroliuojamame tyrime, kuriame palygintos 2 pacientų grupės, kurioms diagnozuotas II–III stadijos keratokonusas: intervencijos grupės pacientams implantuoti intrarageninių žiedų segmentai (Keraring), o kontrolinės grupės pacientams taip pat implantuoti intrarageninių žiedų segmentai (Keraring), tačiau po mėnesio jiems papildomai atlikta ragenos sustiprinimo procedūra. Šiame tyrime abiems pacientų grupėms tiek galutinis UCVA, tiek galutinis BCVA statistiškai reikšmingai pagerėjo lyginant su priešoperacinėmis reikšmėmis ($p<0.001$). Vis dėlto, nebuvo jokio statistinio reikšmingumo tarp pacientų grupių, vertinant tiek UCVA, tiek BCVA pagerėjimą ($p=0.2$). **(D0005)**

Remiantis turimais duomenimis, pakartotinių operacijų reikėjo nuo 4% iki 23% akių, kuriose buvo implantuoti intrarageniniai žiedai/ žiedų segmentai. Vis dėlto, kuo didesnis pakartotinių operacijų dažnis, tuo sunkiau sustabdyti arba sulėtinti ligos progresavimą. **(D0006)**

Organizmo funkcijos

Keratokonusas ir jo gydymas intrarageniniais implantais paveikia tik akis. Poveikis regėjimo aštrumui buvo pateiktas „Sergamumo“ skiltyje. **(D0011)**

Poveikis kasdienio gyvenimo veikloms, naudojant intrarageninius implantus, buvo matuojamas atsižvelgiant į „hospitalizacijos trukmę“ arba į „grįžimą į normalų gyvenimą“. Deja, nė vienas rodiklis nebuvo aptariamas atrinktuose tyrimuose.

Su sveikata susijusi gyvenimo kokybė

Su regėjimu susijusi gyvenimo kokybė buvo analizuota dviejuose vienpusiuose tyrimuose. Viename tyrime su regėjimu susijusi gyvenimo kokybė pagerėjo 88.5% pacientų, o pablogėjo – 11.5% pacientų (regėjimo funkcijos indekso testas). Kitame tyrime pacientai buvo prašomi įvertinti savo matymo kokybę kaip „prastą“, „neblogą“, „gerą“ ar „puikią“. Prieš implantaciją 70% pacientų savo regėjimo kokybę įvertino kaip „prastą“ ir nė vienas neįvertino „puikiai“. Praėjus 6 mėn. po implantacijos, 24% pacientų savo regėjimo kokybę įvertino kaip „prastą“, tačiau 9% pacientų – kaip „puikią“. **(D0013)**

Pacientų pasitenkinimas operacija ir jos rezultatais buvo aptariamas viename vienpusiame tyrime. Minėto tyrimo duomenimis, 73% pacientų po implantacijos buvo labiau, o 8% pacientų mažiau patenkinti savo regėjimu. **(D0017)**

SVEIKATOS TECNOLOGIJOS FUNKCINĖ VERTĖ

Vadovaujantis Ligų, vaistinių preparatų ir medicinos pagalbos priemonių įrašymo į kompensavimo sąrašus ir jų keitimo tvarkos aprašu, patvirtintu Lietuvos Respublikos sveikatos apsaugos ministro 2002 m. balandžio 5 d. įsakymu Nr. 159 „Dėl Ligų, vaistinių preparatų ir medicinos pagalbos priemonių įrašymo į kompensavimo sąrašus ir jų keitimo tvarkos aprašo patvirtinimo“, buvo įvertinta šios sveikatos technologijos – intrastrominių ragenos implantų – kaip medicinos pagalbos priemonės (MPP), funkcinė vertė. Intrastrominių ragenos implantų funkcinė vertė buvo vertinta keratokonuso ir jatrogeninės ragenos ektazijos, atsiradusios po LASIK operacijos, atvejais (1 lentelė).

1 lentelė. Intrastrominių ragenos implantų funkcinė vertė.

Funkcinės vertės kriterijai	**Balai**	**Pastabos**
Ligos įtaka sveikatai	1	Ankstyvųjų stadijų keratokonusas ir ragenos ektazija daro įtaką gyvenimo kokybei. Progresavusi liga gali daryti įtaką neįgalumui ar darbingumui.
Socialinė MPP svarba	1	Intrastrominiai ragenos žiedai pagerina tiek gyvenimo kokybę, tiek regėjimo aštrumą, tačiau nėra duomenų apie prarastų funkcijų atkūrimą.
MPP įnovatyvumas	1	Intrastrominiai ragenos žiedai iš dalies pakeistų šiuo metu naudojamą alternatyvią MPP, tačiau būtų taikoma tik kai kurioms indikacijoms.
MPP klinikinis efektyvumas	0	Nėra įrodymų, lyginančių intrastrominių ragenos žiedų efektyvumą su alternatyvia MPP.
MPP ekonominis efektyvumas	0*	Nėra įrodymų, lyginančių intrastrominių ragenos žiedų efektyvumą su alternatyvia MPP, tačiau alternatyvios MPP kaina yra aukštesnė.
Galutinis balas	**3**	

*Ekonominio efektyvumo aspektas nebuvo vertintas, tačiau intrastrominiams ragenos implantams naudojamų priemonių kaina yra mažesnė negu ragenos transplantacijai.

IŠVADOS

1. Tiek keratokonusas, tiek jatrogeninė ragenos ektazija, atsiradusi po refrakcinės (LASIK) operacijos, yra retos būklės (sergamumas <2 atv./10,000 žm.), prasidedančios paauglystėje/ jaunystėje (amžiaus mediana – 25 m.). Tikėtina ragenos išsigaubimo (ir su tuo susijusio regėjimo aštrumo sumažėjimo) priežastis yra genetinių veiksnių ir ragenos anatominės destabilizacijos derinys.

2. Yra penkios intrarageninių žiedų/ žiedų segmentų rūšys, gavusios CE ženklinimą, tačiau šiuo metu rinkoje yra prieinamos keturios: Ferrara RingTM (AJL OPHTHALMIC S.A., Ispanija), Intacs® ir Intacs® SK (AJL OPHTHALMIC S.A., Ispanija), Keraring-Intrastromal corneal ring (Mediphacos, Brazilija), MyoRing® (DIOPTEX, Austrija). Publikacijose minima ir dar viena rūšis (Bisantis Segments (Optikon 2000 SpA ir Soleko SpA, Italija)), tačiau panašu, jog pirmosios kartos implantai yra nebegaminami. Pagrindinis skirtumas tarp šių gaminių yra implantų dizainas – tik MyoRing® implantai yra pilno žiedo formos, kiti – žiedo segmentai.

3. Bendras nepageidaujamų atvejų dažnis po implantacijos procedūrų vienpusiuose tyrimuose įvyksta 7–16% akių. Implantacijos metu įvykstantys nepageidaujami įvykiai, tokie kaip sudėtingas specialaus tunelio ragenoje suformavimas ar priekinės stromos dalies perforacija, įvyksta 0–2% akių. Pooperaciniai nepageidaujami įvykiai įvyksta 2–23% gydytų akių, pvz., intrarageninio implanto išstūmimas ar pasislinkimas iš implantacijos vietos, infekcija ar ragenos perforacija.

4. Pakartotinių operacijų dažnis siekia 4–23% akių, tačiau kuo didesnis pakartotinių operacijų dažnis, tuo sunkiau sustabdyti arba sulėtinti keratokonuso ar jatrogeninės ektazijos progresavimą. Vis dėlto, pagrindinis intrarageninių žiedų segmentų implantacijos pranašumas prieš kitas chirurgines intervencijas (pvz., ragenos transplantaciją) – esant poreikiui, sąlyginai nesudėtingas implantų pašalinimas.

5. Lyginant regėjimo aštrumą prieš intrarageninių žiedų/ žiedų segmentų implantaciją ir po jos, regėjimo aštrumas pagerėjo daugeliui pacientų: nekoreguotas regėjimo aštrumas po 12 mėn. pagerėjo 70–80% gydytų akių, pablogėjo – mažiau nei 10%; po 24 mėn. pagerėjo 81%, pablogėjo 4–12% gydytų akių; geriausias koreguotas regėjimo aštrumas po 12 mėn. pagerėjo 60–85% gydytų akių, pablogėjo 5%; po 24 mėn. pagerėjo 68%, pablogėjo 15% gydytų akių. Su regėjimu susijusi gyvenimo kokybė pagerėjo apie 88.5%, pablogėjo – apie 11.5% pacientų. Po implantacijos 73% pacientų buvo labiau, o 8% – mažiau, patenkinti savo regėjimu.

REKOMENDACIJOS

1. Šiuo metu turimų įrodymų nepakanka, kad būtų galima įrodyti, jog intrastrominiai ragenos implantai yra efektyvesni ir saugesni nei ragenos transplantacija ar jokio gydymo netaikymas, koreguojant keratokonuso arba jatrogeninės ragenos ektazijos, atsiradusios po LASIK operacijos, pakitimus. Remiantis vienpusiais tyrimais ir lyginant pacientų regėjimo aštrumą prieš ir po implantacijos procedūros pastebėta, jog po intrastrominių žiedų/ žiedų segmentų implantacijos daugelio pacientų regėjimo aštrumas kliniškai pagerėjo.

2. Dėl minimalaus invaziškumo bei galimybės pašalinti implantus intrastrominių ragenos žiedų/ žiedų segmentų implantaciją verta aptarti prieš atliekant ragenos transplantacijos operaciją, tačiau būtina atsižvelgti į apribojimus:
   - Kontaktinių lęšių netoleravimas (arba pacientas nebegali toliau naudoti kontaktinių lęšių);
   - Individualios indikacijos/ kontraindikacijos (pvz.: pakankamas ragenos storis), naudojant intrastrominius ragenos implantus;
   - Intrastrominių ragenos implantų operacijos gali būti atliekamos tik respublikinio lygio ligoninėse;
   - Nepageidaujamų įvykių, susijusių su intrastrominių ragenos implantų, taikomų ektazinių ragenos pakitimų korekcijai, registravimas. Duomenys gali būti naudojami siekiant pakeisti intrastrominių ragenos implantų naudojimo rekomendacijas.

SUMMARY

Scope

PICO for Intrastromal corneal implants	
Population	Patients with: • Keratoconus (ICD-10 code: H18.6) ✓ who are not able to wear glasses or contact lenses (due to intolerance) or ✓ who show an unsatisfactory visual acuity with glasses or contact lenses • Post-LASIK[4] iatrogenic corneal ectasia (ICD-10 code: Q13.4[5]). *MeSH-terms: C11 Eye Diseases, C11.204 Corneal Diseases, C11.204.627 Keratoconus*
Intervention	Intracorneal ring segments (ICRS) or intracorneal rings or intrastromal corneal rings or intrastromal corneal implants. Product names: Ferrara RingTM (Ferrara OphthalmicsTM); Intacs® (Addition TechnologyTM); Keraring (Mediphacos); MyoRing® (DIOPTEX); [Bisantis Segments (Optikon), probably not available anymore]. *MeSH-terms: E07.695 Prostheses and Implants, E07.695.225 Eye, Artificial.*
Comparison	• Corneal transplantation; • No intervention.[6]
Outcomes	
Efficacy	• Length of hospital stay (or time to work resumption); • Quality of life (health- or vision-related); • Re-operation rate; • Patient satisfaction; • Change of visual acuity.
Safety	• Adverse events (intra- and post-operative).
Study design	
Efficacy	• Randomised controlled trials; • Prospective non-randomised controlled trials; • Prospective single-arm studies (with 50 and more eyes).
Safety	• Randomised controlled trials; • Prospective non-randomised controlled trials; • Prospective single-arm studies (with 50 and more eyes).
PICO research question: Is intrastromal corneal implants for patients with keratoconus who are not able to wear glasses or contact lenses (due to intolerance) or who show an unsatisfactory visual acuity with glasses or contact lenses or patients with Post-LASIK iatrogenic corneal ectasia more effective and safer concerning change of visual acuity, length of hospital stay, quality of life, re-operation rate and adverse events than corneal transplantation or no intervention?	

[4] Laser-assisted in situ keratomileusis.

[5] LBI-HTA specialists chose ICD-10 code Q13.4 meaning that post-LASIK iatrogenic corneal ectasia is a congenital disorder. However, VASPVT specialists chose code H18.7 (other and unspecified corneal deformities) instead.

[6] In addition, "no intervention" was considered as comparator. This decision was made, just in case there are no appropriate controlled trials.

Target condition

Keratoconus is a non-inflammatory, often bilateral, corneal ectasia, characterised by a progressive increase in corneal curvature and thinning of the corneal stroma that may or may not lead to irregular astigmatism with an associated decrease in visual acuity. Eventually, an obvious cone-shaped protrusion of the corneal surface may develop. Post-LASIK corneal ectasia is a rare, but serious complication of LASIK (after refractive surgery). The condition is similar to keratoconus where the cornea starts to bulge forwards at a variable time after LASIK. **(A0002)**

The pathophysiology of keratoconus is not well known. Genetic factors appear to be multifactorial and are considered fundamental to the aetiology and progression of keratoconus. Cause of corneal ectasia is probably related to a combination of an intrinsic predisposition to ectasia and an additional anatomical destabilising effect from the refractive surgery. Secondary induced ectasia may be caused by a pure mechanical process (and can be unilateral). While ectasia certainly can occur after many different refractive surgeries, the greatest concern appears to be after LASIK. **(A0003)**

Keratoconus often occurs during teenage years (median age of 25 years) and classically progresses until the 30th or 40th year of life. The decrease in visual acuity is often accompanied by thinning of the cornea, glare intolerance, photophobia and ocular irritation. Corneal ectasia is one of the most devastating complications after LASIK. Ectatic changes can occur as early as one week or can be delayed up to several years after LASIK. In addition, LASIK permanently thins and weakens the cornea, which may lead to progressive steepening or bulging (ectasia) of the cornea with associated deterioration of vision. **(A0004; A0005)**

Target population

The target population is patients with keratoconus (mainly stages 1–3) or post-LASIK corneal ectasia that are contact lens intolerant (patients with keratoconus), have an adequate corneal thickness, particularly around the area of the implant incision site, and are without central corneal scarring. **(A0007)**

Keratoconus is associated with a low incidence of 2 per 100,000 people per year and a prevalence has been reported to vary from <10 to >50 cases per 100,000. The actual incidence of post-LASIK corneal ectasia is unknown, although the reported incidence rate is less than 1% of patients who underwent LASIK. In 2015, a total of 16,509 inpatient surgical interventions were performed in Lithuania on the cornea, iris or lens. **(A0005; A0006; A0011)**

Due to low prevalence rates of both indications, the estimated consequences for society do not seem considerable, but are so for the affected patients. Hence, both diseases implicate limitations in the quality of life up to disability. **(A0005; A0006)**

Current management of the condition

In early stages of keratoconus and post-LASIK corneal ectasia, computerised corneal topography techniques using curvature-based analysis and newer forms of elevation-based tomography appear to be the most sensitive and widely available methods for detecting early keratoconus. However, there seems to be no universally diagnostic criterion to diagnose early forms of the disease. **(A0024)**

In patients with intermediately progressed keratoconus or post-LASIK corneal ectasia, computerised corneal topography and elevation-based tomography are probably the most widely used diagnosing methods. In more advanced cases, the diseases can be diagnosed by characteristic slit lamp findings. **(A0024)**

There are no drugs known to reverse or prevent keratoconus. However, patients may slow the disease progression by refraining from rubbing their eyes. Early in the process of keratoconus (mild to moderate), the visual impairment is usually correctable with soft contact lenses, spectacles and in some cases intracorneal ring segment implantation. As the disease progresses, it is more difficult to refract the patient to a clear visual acuity with soft contact lenses or spectacles and corneal surgery, including deep lamellar keratoplasty or penetrating keratoplasty, may be needed. **(A0025)**

At the intermediate stage, patients usually experience vision loss that is no longer correctable with soft contact lenses or spectacles. The increasing irregularity of the astigmatism may call for rigid, gas-permeable contacts in order to achieve clear vision. Some patients require a scleral lens or a piggyback configuration consisting of hard contact lenses worn over soft lenses to achieve adequate fit, comfort and vision. For patients who progress to more advanced stages (stage 2 and more) of the disease, contact lens wear may become increasingly difficult and often uncomfortable due to the steepness of the cornea and difficulty in fitting the lenses. Contact lens intolerance is a common indication for corneal transplantation at this stage. **(A0025)**

Treatment options for post-LASIK corneal ectasia are the same as for keratoconus. **(A0025)**

Regulatory status

Initially, intrastromal corneal implants were developed for the treatment of myopia and several products received market authorisation in Europe (CE marking) for this indication. Therefore, intrastromal corneal implants never achieved commercial success for the treatment of myopia. In addition, intrastromal corneal implants were also considered to be a therapeutic alternative for the correction of ectatic corneal disorders such as keratoconus and post-LASIK corneal ectasia. **(A0020)**

Thereafter, five products of intrastromal corneal implants are marketed by five manufacturers and approved by the Communauté Européenne (CE) for the treatment of keratoconus (and post-LASIK ectasia). Intacs® is also approved by the US FDA – however, as a Humanitarian Use Device (HUD). **(A0020)**

Actually, the use of intrastromal corneal implants for the treatment of keratoconus or post-LASIK corneal ectasia is not included in the Lithuanian reimbursement system. However, the insertion operation is reimbursed by the Lithuanian health care system according to the DRG. **(A0021)**

Features of the technology

Corneal implants are small segments of rings or full rings of synthetic material (e.g., polymethyl methacrylate or acrylic polymers) that are implanted in the corneal stroma to achieve flattening of the surface in patients with mild to moderate keratoconus. The rings are implanted in channels created mechanically or by means of a laser.

Five products of intrastromal corneal implants are marketed by manufacturers. However, it seems very likely that the first generation implants Bisantis Segments (Optikon 2000 SpA and Soleko SpA, Italy) are not available anymore, since the manufacturer‘s website could not be identified (access date: 25th July 2016). Four main types of intracorneal segments are these:

- Ferrara RingTM (AJL OPHTHALMIC S.A., Spain);

- Intacs® and Intacs® SK (AJL OPHTHALMIC S.A., Spain);
- Keraring-Intrastromal corneal ring (Mediphacos, Brazil);
- MyoRing® (DIOPTEX, Austria). **(B0001)**

The main difference between these products is their design (full rings or segments) with different shapes, diameters and thicknesses. Only MyoRing® is a full ring.

Since the early 1990s for myopia and since 2004 for ectatic corneal disorders, intrastromal corneal implants have been sold and in use. Thus, the device is not in a phase of development anymore and – more or less – fully developed. Similarly, corneal transplantation has already been in use for many decades and is a well-established technique. **(B0003)**

The main expected advantage of intrastromal corneal implants over other surgical interventions like corneal transplantation is that the implants can be removed relatively easily. This allows a (partial) reversal of the correction or the replacement with different rings to further adapt the needed correction.

Furthermore, the intervention is a minimally invasive surgical option. Thus, a possibly resulting strength is that patients are allowed to quickly resume work or normal activities, as compared to corneal transplantation. **(B0001; B0002)**

The implantation of intrastromal corneal implants should be performed by an eye surgeon (or corneal surgeon) with the support of two persons of the nursing staff. The procedure can be done under topical or general anaesthetics in an inpatient setting or in an outpatient facility. **(B0004)**

Generally, optical corrections, such as contact lenses (used in early stages of keratoconus) and corneal transplantation, are treatment options for ectatic corneal disorders. However, intrastromal corneal implants are indicated when patients show contact lens intolerance (preferably in the absence of corneal disorders). **(B0001)**

Collagen corneal cross-linking (CXL) is a relatively new treatment option that is supposed to slow the progression of the disease. Crosslinking can be defined as the creation of bonds that connect 1 polymer chain to another. CXL uses a combination of riboflavin (vitamin B2) and ultraviolet-A (UVA) light to strengthen the corneal tissue through photosensitization and chemical cross-linking. Riboflavin acts as a photosensitizer and absorbs the UVA radiation to limit the depth of the treatment effect. During the photosensitizing process, free radicals are produced, which cause formation of chemical bonds within the corneal stroma resulting in corneal strengthening. Sometimes the procedure is used in combination with other interventions such as ICRS implantation or photorefractive keratectomy (PRK). **(B0001)**

In patients with advanced keratoconus with stromal scarring in the visual axis, treatment options such as contact lenses or ICRS may fail to improve the corrected visual acuity often requiring keratoplasty, either lamellar or full thickness, depending on the extent of the stromal scar. Corneal transplantation, also known as corneal grafting, consists in the replacement of the diseased cornea by corneal tissues from a suitable, deceased donor. **(B0001)**

Investments and tools required to use the technology

For intrastromal corneal implants as well as corneal transplantation a sterile operation theatre is suggested. **(B0008; B0009)**

In addition, for the implantation of intrastromal corneal implants, a channel has to be created to insert the device. This can be done with a femtosecond laser or mechanically; thus, several instruments are needed for the intervention (e.g., a Sinsky hook, a knife, semi-automated suction ring, etc.). **(B0008; B0009)**

Patient safety

No studies were identified that are directly comparing the implantation of intrastromal corneal implants with corneal transplantation (e.g., keratoplasty) or no intervention for the treatment of keratoconus. **(C0008)**

However, 1 prospective randomized study was identified, which compared the intervention group of patients that underwent the implantation of intrastromal corneal rings (Keraring) with the control group of patients who also had the implantation of intrastromal corneal rings (Keraring) but one month later TE-CXL was performed as well. Extrusion of Kerarings occurred in 1 eye because of implant erosion. Unfortunately, the case was excluded from the study and it is unknown which group of patients experienced this complication. **(C0008)**

In the single-arm studies, general adverse events occurred in 7 to 16% of the eyes. Intra-operative adverse events, like difficulties in forming the intrastromal tunnel to implant the rings or anterior perforation, occurred in 0–2% of the eyes. Post-operative adverse events occurred in 2 to 23% of the treated eyes e.g., extrusion or migration of a segment, external infection or corneal perforation. **(C0008)**

No direct evidence was found to answer the question about how the frequency or severity of harms change over time or in different settings in an appropriate way. However, it seems likely that the frequency and/or severity of harms slightly increase over time. **(C0004)**

No direct evidence was found to answer the question about the susceptible patient groups that are more likely to be harmed through the use of the intrastromal corneal implants. Also, no direct evidence was found to answer the research question about the association with user-dependent harms. However, in all included studies intrastromal corneal implants were implanted by experienced eye surgeons. **(C0005; C0007)**

Mortality

Mortality is not a relevant outcome for assessing the clinical effectiveness of intrastromal corneal implants, since neither the disease nor the intervention is life-threatening. **(D0001)**

Morbidity

The change of visual acuity of one and more Snellen lines was reported in four single-arm studies. After 12 months, UCVA was improved in around 70–80% of eyes and worsened in less than 10% of eyes; after 24 months, improved in 81% and worsened in 5% of treated eyes. Similarly, BCVA after 12 months improved in 60–85% and worsened in 4–12% of the treated eyes; after 24 months, 68% improved, 15% worsened. **(D0005)**

The change of visual acuity of two or more Snellen lines after treatment was reported in one single-arm study for UCVA and in two single-arm studies for BCVA. After 6 months, UCVA improved in 79% and worsened in none of the treated eyes. In addition, BCVA after 6 months improved in 39–62% and worsened in 6-12% of eyes; after 12 months, 42% improved, 8% worsened. **(D0005)**

The change of visual acuity was reported in RCT, where the intervention group of patients that underwent the implantation of intrastromal corneal rings (Kerarings) for the treatment of grades II-III

of keratoconus was compared with the control group of patients who also had the implantation of intrastromal corneal rings (Keraring) for the treatment of grades II–III of keratoconus and one month later the corneal transepithelial collagen cross-linking (TE-CXL) was performed. There was a statistically significant improvement in the final UCVA and in the final BCVA from the preoperative values in both groups ($p<0.001$). However, there was no statistically significant difference between groups regarding the UCVA improvement ($p=0.2$) and regarding the improvement in BCVA ($p=0.2$). **(D0005)**

According to the available data, between 4 and 23% of the eyes with an implanted intrastromal corneal ring had to be re-operated. Thus, the higher the re-operation rate, the lower the chance of stopping or slowing the progression. **(D0006)**

Function

Keratoconus and the treatment with intrastromal corneal implants exclusively affect the eyes and not the whole body. The effect on visual acuity (the only affected body function) has already been addressed in the previous section. **(D0011)**

Activities of daily living using intrastromal corneal implants were estimated in accordance with "length of hospital stay (or time to resume work/normal activities)". However, the outcome was not reported in any of the identified studies.

Health related quality of life

Vision-related quality of life was reported in two single-arm studies. In one study, vision-related quality of life improved in 88.5% and worsened in 11.5% of patients, measured with the Visual Function-7 score (no information on this questionnaire was presented). In another study, the quality of vision was measured with the characteristics "poor", "fair", "good" and "excellent" by asking the patients. Before implantation, 70% of patients had a "poor", and none had an "excellent" quality of vision. At 6 months after implantation, 24% of patients had "poor" and 9% of patients had "excellent" quality of vision. **(D0013)**

The "patient satisfaction" outcome was reported in one of the identified single-arm studies as the change of self-reported satisfaction with vision. According to that study, 73% of patients reported an improvement in satisfaction and 8% reported a worsening of satisfaction with their vision. **(D0017)**

HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

Research questions [1]

ID	Question
A0001	For which health conditions, and for what purposes are intrastromal corneal implants used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for keratoconus or post-LASIK corneal ectasia?
A0004	What is the natural course of keratoconus or post-LASIK corneal ectasia?
A0005	What is the burden of keratoconus or post-LASIK corneal ectasia?
A0006	What are the consequences of keratoconus or post-LASIK corneal ectasia for society?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are intrastromal corneal implants utilised?
A0020	For which indications have intrastromal corneal implants received marketing authorisation or CE marking?
A0021	What is the reimbursement status of intrastromal corneal implants?
A0024	How is keratoconus or post-LASIK corneal ectasia currently diagnosed according to published guidelines and in practice?
A0025	How is keratoconus or post-LASIK corneal ectasia currently managed according to published guidelines and in practice?

A0001. For which health conditions, and for what purposes is intrastromal corneal implants used?

Originally, intrastromal corneal rings (ICRS) were developed for the treatment of myopia. Later, intrastromal corneal implants were also considered for the correction of ectatic corneal disorders such as keratoconus and post-LASIK corneal ectasia [2,3]. Intrastromal corneal rings (Intacs, Ferrara, Kerarings) are small devices that can be implanted into the cornea in an attempt to flatten the corneal profile to achieve a better uncorrected visual acuity and to enhance contact lens tolerance [4]. Also, ICRS attempt to regularize the biomechanical status in the underlying stroma (52% stabilizing, 45% regression with 3% progression despite treatment [5].

A0002. What is the disease or health condition in the scope of this assessment?

This assessment will exclusively focus on the treatment of keratoconus and post-LASIK corneal ectasia.

Keratoconus is a non-inflammatory, often bilateral, corneal ectasia, characterised by a progressive increase in corneal curvature and thinning of the corneal stroma that may or may not lead to irregular astigmatism with an associated decrease in visual acuity [6]. Eventually, an obvious cone-shaped protrusion of the corneal surface may develop [7].

Post-LASIK corneal ectasia is a rare, but serious complication of LASIK (after refractive surgery). The condition is similar to keratoconus where the cornea starts to bulge forwards at a variable time after LASIK. The disease is mainly manifested by progressive corneal steepening, an increase in myopia (short-sightedness), corneal aberrations, plus astigmatism and the loss of visual acuity [2].

A0003. What are the known risk factors for keratoconus or post-LASIK corneal ectasia?

The pathophysiology of *keratoconus* is not well known. Genetic factors appear to be multifactorial and are considered fundamental to the aetiology and progression of keratoconus. However, the underlying molecular and/ or genetic abnormalities are unknown [7,8].

Keratoconus has been linked with systemic conditions such as atopic disease, genetic conditions such as trisomy 21 and Turner's syndrome, and various connective tissue disorders, as well as with eye rubbing, rigid contact lens wear and ocular trauma [7,9]. In addition, keratoconic corneas also have an accumulation of cytotoxic byproducts, abnormal antioxidant enzymes and increased levels of mitochondrial DNA damage. This suggests that ongoing oxidative stress contributes to keratoconus [7].

In global consensus on Keratoconus and Ectatic diseases an agreement on risk factors for keratoconus was generated. The pathophysiology of keratoconus is likely to include the following components: Genetic disorders; Biochemical disorders; Biomechanical disorders; Environmental disorders [10]. It was also agreed that these risk factors should be considered for keratoconus: Down syndrome, relatives of affected patients especially if they are young, ocular allergy, ethnic factors (Asian and Arabian), mechanical factors, e.g., eye rubbing, floppy eyelid syndrome, atopy, connective tissue disorders (Marfan syndrome), Ehlers–Danlos syndrome and Leber congenital amaurosis [10]

Cause of *corneal ectasia* is probably related to a combination of an intrinsic predisposition to ectasia and an additional anatomical destabilising effect from the refractive surgery. Secondary induced ectasia may be caused by a pure mechanical process (and can be unilateral) [10]. While ectasia certainly can occur after many different refractive surgeries, the greatest concern appears to be after LASIK [11]. Risk factors of *post-LASIK corneal ectasia* can be abnormal preoperative topography, low residual stromal bed (RSB) thickness, young age, low preoperative corneal thickness and/or high myopia, steep keratometry readings, oblique cylinder, thin pachymetry, posterior surface elevation on corneal tomography, greater inferior-superior ratio, and abnormal best-fit-sphere. The importance of each of these factors is unclear [2,11,12].

A0004. What is the natural course of keratoconus or post-LASIK corneal ectasia?

The underlying disease process in keratoconus is far from fully established. As already outlined, there is a clear genetic predisposition associated with changes that include corneal thinning and protrusion [9]. *Keratoconus* often occurs during teenage years and classically progresses until the 30th or 40th year of life. Vigorous eye rubbing may lead to more rapid progression of the disease [13].

Keratoconus affects both genders, but it is unclear whether any significant difference exists between males and females [6]. Many affected individuals experience an arrest of the disease's progression or probably a reduction in the rate of progression [7]. The decrease in visual acuity is often accompanied by glare intolerance, photophobia and ocular irritation [13].

Keratoconus has four stages, based on Amsler-Krumeich's classification system (see table below). However, currently there is no clinically adequate classification system for keratoconus [10].

Table 2. Amsler-Krumeich's classification system [8,14].

Grade	Characteristics
1	Eccentric corneal steepening Induced myopia and/or astigmatism <5 D (dioptre) Mean central K readings ≤48 D Vogt's striae, no scars

2	Induced myopia and/or astigmatism >5 D ≤8 D Mean central K readings ≤53 D Absence of scarring Corneal thickness ≥400 μm
3	Induced myopia and/or astigmatism >8 D <10 D Mean central K readings >53 D Absence of scarring Corneal thickness 200 to 400 μm
4	Refraction not measurable Mean central K readings >55 D Central corneal scarring perforation Corneal thickness ≤200 μm

Corneal ectasia is one of the most devastating complications after LASIK. The disease is defined in patients who developed increasing myopia, with or without increasing astigmatism, loss of uncorrected visual acuity, often loss of best-corrected visual acuity, with keratometric steepening, with or without central and paracentral corneal thinning, and topographic evidence of asymmetric inferior corneal steepening after LASIK procedure. Ectatic changes can occur as early as one week or can be delayed up to several years after LASIK [2,12].

Effects of the disease or health condition on the individual and society

A0005. What is the burden of keratoconus or post-LASIK corneal ectasia?

Due to the thinning of the cornea, *keratoconus* can lead to irregular astigmatism and decrease in visual acuity [6,7]. Furthermore, keratoconus is unique among chronic eye diseases as it has an early age of onset (median age of 25 years) [8].

In addition, LASIK permanently thins and weakens the cornea, which may lead to progressive steepening or bulging (*ectasia*) of the cornea with associated deterioration of vision [12,15].

Hence, both diseases implicate limitations in the quality of life up to disability [6,7,16].

A0006. What are the consequences of keratoconus or post-LASIK corneal ectasia for society?

Keratoconus is associated with a low incidence of 2 per 100,000 people per year and a prevalence has been reported to vary from <10 to >50 cases per 100,000 and is frequently quoted as approximately 1 per 2,000 people (or 5 per 10,000) [8,9,16,17]. Conversely, in high prevalence areas such as the Middle East, topographic features of keratoconus have been noted in 3.3% of a young adult population. This wide variation in reported prevalence is in part due to different genetic predisposition, differing exposure to cofactors, and perhaps most importantly different diagnostic criteria [9]. Thus, keratoconus is defined as a rare disease.

The actual incidence of *post-LASIK corneal ectasia* is unknown, although the reported incidence rate is less than 1% of patients who underwent LASIK [12].

However, the data about incidence and prevalence of keratoconus (ICD-10-AM: H18.6) and post-LASIK corneal ectasia (ICD-10-AM: H18.7) in Lithuania are not available.

Due to low prevalence rates of both indications, the estimated consequences for society do not seem considerable, but are so for the affected patients [8,18].

Target population

A0007. What is the target population in this assessment?

The target population is patients with keratoconus (mainly stages 1–3) or post-LASIK corneal ectasia that are contact lens intolerant (patients with keratoconus), have an adequate corneal thickness, particularly around the area of the implant incision site, and are without central corneal scarring [3]. [8].

A0023. How many people belong to the target population?

This question has been defined as not relevant for this report.

A0011. How much is intrastromal corneal implants utilised?

Based on the information from LBI-HTA decision support document No. 85 ("Intrastromal corneal implants for ectatic corneal disorders") [19], the estimated annual utilization of the intrastromal corneal rings technology in Austria is around 200. In 2013, a total of 110,210 inpatient surgical interventions were performed in Austria on the cornea, iris or lens [19].

In 2015, a total of 16,509 inpatient surgical interventions were performed in Lithuania on the cornea, iris or lens [20].

Regulatory & reimbursement status

A0020. For which indications have intrastromal corneal implants received marketing authorisation or CE marking?

Initially, intrastromal corneal implants were developed for the treatment of myopia and several products received market authorisation in Europe (CE marking) for this indication. However, at the same time another intervention for this disease arose and overshadowed intrastromal corneal rings: laser-assisted in situ keratomileusis (LASIK). Therefore, intrastromal corneal implants never achieved commercial success for the treatment of myopia [2].

In addition, intrastromal corneal implants were also considered to be a therapeutic alternative for the correction of ectatic corneal disorders such as keratoconus and post-LASIK corneal ectasia [2].

Thereafter, all products of intrastromal corneal implants mentioned at the part B "Description and technical characteristics of the intrastromal corneal implants" that are actually available and approved by the Communauté Européenne (CE) for the treatment of keratoconus (and post-LASIK ectasia). Intacs® is also approved by the US FDA – however, as a Humanitarian Use Device (HUD)[7].

An overview of the different intrastromal corneal ring products based on the information of the manufacturers' websites is listed in the table below.

Table 3. Overview of marketing authorisation of intrastromal corneal rings for keratoconus

Manufacturer	FDA-approval	CE-marking

[7] An HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

Bisantis Segments (Optikon 2000 SpA and Soleko SpA, Italy)	No information found[8]	No information found[9]
Ferrara Ring™ (AJL OPHTHALMIC S.A., Spain)	No	Yes
Intacs® and Intacs® SK (AJL OPHTHALMIC S.A., Spain)	Yes	Yes
Keraring – Intrastromal corneal ring (Mediphacos, Brazil)	No	Yes
MyoRing® (DIOPTEX, Austria)	No	Yes

References: individual manufacturers' websites.

A0021. What is the reimbursement status of intrastromal corneal implants?

Actually, the use of intrastromal corneal implants for the treatment of keratoconus or post-LASIK corneal ectasia is not included in the Lithuanian reimbursement system. However, the insertion operation is reimbursed by the Lithuanian health care system according to the DRG.

Also, the ICRS for the treatment of keratoconus or post-LASIK corneal ectasia is not included in the Austrian hospital benefit catalogue. Therefore, the intervention itself is not reimbursed by the Austrian health care system.

Current clinical management of the disease or health condition

A0024. How is keratoconus or post-LASIK corneal ectasia currently diagnosed according to published guidelines and in practice?

In early stages of *keratoconus* and *post-LASIK corneal ectasia*, computerised corneal topography (CCT) techniques using curvature-based analysis and newer forms of elevation-based tomography appear to be the most sensitive and widely available methods for detecting early keratoconus [8,10,12]. Furthermore, a variety of diagnostic algorithms can help diagnose early keratoconus and corneal ectasia. However, there seems to be no universally diagnostic criterion to diagnose early forms of the disease [12].

In patients with intermediately progressed keratoconus or post-LASIK corneal ectasia, computerised corneal topography and elevation-based tomography are probably the most widely used diagnosing methods [11,12].

In more advanced cases, the diseases can be diagnosed by characteristic slit lamp findings [8,12].

A0025. How is keratoconus or post-LASIK corneal ectasia currently managed according to published guidelines and in practice?

Treatment options for *post-LASIK corneal ectasia* are the same as for *keratoconus*. Therefore, only the treatments for keratoconus are explained – representative for both indications.

[8] Since we could not identify the website of the manufacturer, we were not able to find any information regarding FDA and CE approval.

[9] Since we could not identify the website of the manufacturer, we were not able to find any information regarding FDA and CE approval.

There are no drugs known to reverse or prevent keratoconus. However, patients may slow the disease progression by refraining from rubbing their eyes [7,10,12].

Early in the process of keratoconus (mild to moderate), the visual impairment is usually correctable with soft contact lenses, spectacles and in some cases intracorneal ring segment implantation [7,21]. As the disease progresses, it is more difficult to refract the patient to a clear visual acuity with soft contact lenses or spectacles and corneal surgery, including deep lamellar keratoplasty or penetrating keratoplasty, may be needed [7,21].

At the intermediate stage, patients usually experience vision loss that is no longer correctable with soft contact lenses or spectacles. The increasing irregularity of the astigmatism may call for rigid, gas-permeable contacts in order to achieve clear vision. Some patients require a scleral lens or a piggyback configuration consisting of hard contact lenses worn over soft lenses to achieve adequate fit, comfort and vision [7,17,22].

For patients who progress to more advanced stages (stage 2 and more) of the disease, contact lens wear may become increasingly difficult and often uncomfortable due to the steepness of the cornea and difficulty in fitting the lenses. Contact lens intolerance is a common indication for corneal transplantation at this stage [7,17]:

Penetrating keratoplasty (PK) – a corneal transplantation – is the mainstay of treatment for keratoconus. The procedure applies to be effective with a low rejection rate. In spite of successful surgery, residual corneal astigmatism and refractive error usually require additional correction with a contact lens. In addition, complications after PK can include allograft rejection, a fixed, dilated pupil and, on occasion, recurrence of keratoconus [14,17]. For patients who have moderate keratoconus without significant scarring, there is renewed interest in *deep anterior lamellar keratoplasty* (DALK), especially with the precision, predictability and convenience of the femtosecond laser for these cases. The DALK technique aims to remove nearly all corneal stroma [17,22].

Furthermore, *intrastromal corneal rings* or ring segments are also an option, particularly if the patient demonstrates disease progression with apical displacement. However, several products are not indicated anymore for keratoconus with a certain keratometry (e.g. >70 D for Keraring) [16,17].

Besides, *collagen cross-linking* (CXL) is a relatively new treatment option. CXL involves a one-time application of riboflavin solution to the eye that is activated by illumination with UV light. The riboflavin causes new bonds to form across adjacent collagen strands in the stromal layer of the cornea, which recovers and preserves some of the cornea's mechanical strength, possibly slowing the progression of the disease [17,21,22].

Discussion

Keratoconus and post-LASIK corneal ectasia are rare diseases, affecting 1 per 2,000 people in case of keratoconus and probably less in case of post-LASIK ectasia. Even if both diseases are not common and the impact for society is minor, the diseases severely reduce the quality of life of the persons affected, due to low visual acuity. Furthermore, the diagnosis of the diseases can result in occupational disability in several professions (e.g., police, military and aviation) [19].

Pathophysiology and natural history of keratoconus and post-LASIK corneal ectasia are poorly understood currently there is no clinically adequate classification system for keratoconus [10]. As already outlined, there is a clear genetic predisposition associated with changes that include corneal thinning and protrusion. A 2-hit hypothesis that includes genetic predisposition and environmental factors such as eye rubbing is increasingly accepted. Although generally thought to be non-inflammatory, recent evidence suggests that a low-level inflammatory component may be present, and this long-held presumption may need to be reevaluated [9].

Intracorneal implants for the correction of refractive errors and ectatic corneal diseases can be grouped into 2 categories: (1) intracorneal ring segments of up to 355 degree arc length such as the Ferrara ring (AJL OPHTHALMIC S.A., Spain), Intacs (AJL OPHTHALMIC S.A., Spain), and Keraring (Mediphacos, Brazil) and (2) the intracorneal continuous complete ring MyoRing (Dioptex GmbH, Austria) [23]. Two surgical methods have been described for ICRS implantation: mechanical and femtosecond laser assisted [24].

All products of intrastromal corneal implants are actually available and approved by the Communauté Européenne for the treatment of keratoconus (and post-LASIK ectasia). Thus, the FDA approved one device (Intacs® and supplying products) under the Humanitarian Device Exemption program, by only assessing the safety. That means the product may only be used in facilities that have an institutional review board to supervise clinical testing. The device must be for humanitarian use and the effectiveness of the device for the specific indication does not have to be demonstrated [19].

DESCRIPTION AND TECHNICAL CHARACTERISTICS OF THE INTRASTROMAL CORNEAL IMPLANTS

Research questions [1]

ID	Question
B0001	What are intrastromal corneal implants and the comparators?
B0002	What is the claimed benefit of intrastromal corneal implants in relation to the comparators?
B0003	What is the phase of development and implementation of intrastromal corneal implants and the comparators?
B0004	Who administers intrastromal corneal implants and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use intrastromal corneal implants and the comparators?
B0009	What supplies are needed to use intrastromal corneal implants and the comparators?

Features of the technology and comparators

B0001. What are intrastromal corneal implants and the comparators?

Corneal implants are small segments of rings or full rings of synthetic material (e.g., polymethyl methacrylate or acrylic polymers) that are implanted in the corneal stroma to achieve flattening of the surface in patients with mild to moderate keratoconus. The rings are implanted in channels created mechanically or by means of a laser [2,6,25]. In the mechanical or manual technique, the surgeon must mark the center of the pupil in order to use it as a reference point during the procedure. Then, a calibrated diamond knife is used to create an incision at a depth of 70% of the corneal pachymetry. A suction ring is placed around the corneal limbus in order to fixate the eye during the dissection of the corneal stroma. Two semicircular dissectors are then placed through the incision and advanced in the deep stroma in a clockwise and counter-clockwise movement aiming to perform a tunnel within the corneal lamellas. The other technique used to create the tunnels is with the femtosecond laser. In this case, a coupling interface is placed over the cornea with a disposable device, which allows a precise focus of the laser beam, thus creating a dissection at the desired depth. The tunnel is then created at approximately 70 or 80% of the corneal pachymetry without directly manipulating the eye. Finally, the intracorneal ring segments are inserted in the created tunnels [26].

Five products of intrastromal corneal implants are marketed by manufacturers [2,25]. However, it seems very likely that the first generation implants Bisantis Segments (Optikon 2000 SpA and Soleko SpA, Italy) [27] are not available anymore, since the manufacturer‘s website could not be identified (access date: 25th July 2016). Four main types of intracorneal segments are these [28]:

- Ferrara Ring™ (former Ferrara OphthalmicsTM, Brazil, belongs now to AJL OPHTHALMIC S.A., Spain)[10],
- Intacs® and Intacs® SK (former Addition TechnologyTM, USA, belongs now to AJL OPHTHALMIC S.A., Spain)[11],
- Keraring-Intrastromal corneal ring (Mediphacos, Brazil)[12],

[10] See also http://www.ferrararing.com.br/en/products and http://www.ajlsa.com
[11] See also http://www.additiontechnology.com and http://www.ajlsa.com

- MyoRing® (DIOPTEX, Austria)[13].

The main difference between these products is their design (full rings or segments) with different shapes, diameters and thicknesses [2]. Bisantis Segments, Ferrara RingTM, Intacs® and Keraring are arc segments and therefore called intracorneal ring segments. The MyoRing® is a full ring and therefore called a corneal intrastromal implantation system (CISIS). While ICRS are implanted into a circular tunnel, the MyoRing® is implanted into a corneal pocket through a small corneal incision [23]. In the following, "rings" is used to designate both full rings and ring segments.

Also, Keraring and Ferrara rings are triangular, whereas Intacs® is hexagonal and Intacs® SK is elliptical in shape in crosssection [29]. The different shapes may have an impact on the visual quality as ring segments without sharp angles may cause the least light scattering, resulting in less glare and halos compared with triangular or hexagonal shapes. Similarly, the segment that is implanted closer to the visual axis may result in more visual complaints particularly in dim illumination as it interferes with the pupil [29].

Generally, optical corrections, such as contact lenses (used in early stages of keratoconus) and corneal transplantation, are treatment options for ectatic corneal disorders [17,22]. However, intrastromal corneal implants are indicated when patients show contact lens intolerance (preferably in the absence of corneal disorders) [17].

Collagen corneal cross-linking is a relatively new treatment option that is supposed to slow the progression of the disease [15,22]. Crosslinking can be defined as the creation of bonds that connect 1 polymer chain to another. CXL uses a combination of riboflavin (vitamin B2) and ultraviolet-A (UVA) light to strengthen the corneal tissue through photosensitization and chemical cross-linking. Riboflavin acts as a photosensitizer and absorbs the UVA radiation to limit the depth of the treatment effect. During the photosensitizing process, free radicals are produced, which cause formation of chemical bonds within the corneal stroma resulting in corneal strengthening [24,29]. The standard protocol, or what is now referred to as the Dresden protocol for CXL, requires epithelial removal (epithelium-off CXL), application of riboflavin 0.1% solution for 30 minutes before UVA exposure, with a wavelength of 370 nm and homogenous irradiance of 3 mW/cm^2 for 30 minutes (5.4 J/cm^2) [24]. In epithelium-on (transepithelial) CXL, the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed [21].

Sometimes the procedure is used in combination with other interventions such as ICRS implantation or photorefractive keratectomy (PRK) [21]. The purpose of these combined procedures is to augment the effect of the individual procedure in keratoconus [29].

Corneal transplantation has been used for many decades to treat ectatic corneal disorders and is the most frequent used treatment for ectatic corneal disorders [15,22]. Furthermore, in the description of the application form LBI-HTA received from the Austrian Ministry of Health ("Verwaltung von Änderungsund Ergänzungsvorschlägen zum Leistungskatalog des BMG", VAEV) the only treatment alternative that was mentioned is corneal transplantation. In addition, several papers defined intrastromal corneal implants as an alternative to keratoplasty [3]. Thus, corneal transplantation was chosen as a secondary comparator, even though it is more invasive than the use of intrastromal corneal implants or collagen cross-linking [14,17].

In patients with advanced keratoconus with stromal scarring in the visual axis, treatment options such as contact lenses or ICRS may fail to improve the corrected visual acuity often requiring keratoplasty, either lamellar or full thickness, depending on the extent of the stromal scar [6]. Corneal

[12] See also http://www.mediphacos.com/en/medico/produtos/
[13] See also http://www.dioptex.com/products/myoring-corneal-implant/

transplantation, also known as corneal grafting, consists in the replacement of the diseased cornea by corneal tissues from a suitable, deceased donor. There are several methods of transplantations: e.g., penetrating keratoplasty designates the transplantation of the entire corneal tissue, deep anterior lamellar keratoplasty the transplantation of the anterior corneal layers while preserving Descement's membrane and endothelium [17,22].

In addition, "no intervention" was considered as a tertiary comparator besides corneal collagen cross-linking and corneal transplantation.

B0002. What is the claimed benefit of intrastromal corneal implants in relation to the comparators?

Intrastromal corneal implants for the treatment of keratoconus and post-LASIK corneal ectasia are intended to improve visual acuity – like corneal transplantation as well [8,17].

The main expected advantage of intrastromal corneal implants over other surgical interventions like corneal transplantation is that the implants can be removed relatively easily. This allows a (partial) reversal of the correction or the replacement with different rings to further adapt the needed correction [22,30,31]. Before re-operating, it is necessary to wait at least three months after segment removal for the cornea to revert back to its original shape [31].

Furthermore, the intervention is a minimally invasive surgical option. Thus, a possibly resulting strength is that patients are allowed to quickly resume work or normal activities, as compared to corneal transplantation [2,30].

The benefits of CXL procedure found by NICE (National Institute for Health and Care Excellence), showed: improved keratoconus, clearer eyesight, and astigmatism. Also, when combined with other procedures CXL improved keratoconus and influenced clearer eyesight [21].

A major issue of corneal transplantation is that an adequate donor is required. This implicates waiting times, the matching of human leukocyte antigen (HLA), the use of immunosuppressive drugs (even only local), the life expectancy of the transplant (approximately ten years) and a more complicated reoperation [14,15,17,22].

Since corneal transplantation is a more invasive intervention, it entails higher intra-operative and post-operative risks as well as higher risks for secondary trauma due to a weakening of the structure of the eye ball [14,15,17,22].

B0003. What is the phase of development and implementation of intrastromal corneal implants and the comparators?

Intracorneal segments were initially designed for merely refractive purposes for patients not affected with keratoconus; however, this technique is now primarily used to remodel corneal shape in eyes with corneal ectasia [28].

Since the early 1990s for myopia and since 2004 for ectatic corneal disorders, intrastromal corneal implants have been sold and in use. Thus, the device is not in a phase of development anymore and – more or less – fully developed. Similarly, corneal transplantation has already been in use for many decades and is a well-established technique [17,25,32].

Corneal CXL use dates back to 1997 but it did not begin to be used in a standardized fashion until 2007 within the private sector, including recognition by health insurers, and also became available in the New Zealand public health sector in 2014, following the standard protocol which has become known as the Dresden protocol [9,28].

Administration, investments, personnel and tools required to use the technology and the comparator(s)

B0004. Who administers intrastromal corneal implants and the comparators and in what context and level of care are they provided?

The implantation of intrastromal corneal implants should be performed by an eye surgeon (or corneal surgeon) with the support of two persons of the nursing staff. The procedure can be done under topical or general anaesthetics in an inpatient setting or in an outpatient facility [8,17,30].

The CXL procedures are normally done as outpatient procedures using topical anaesthesia, and typically take 60–90 minutes. The procedures should only be carried out by ophthalmologists with expertise in managing corneal disease and specific training in the use of ultraviolet light or by appropriately trained staff under their supervision [21].

For the corneal transplantation, general anaesthesia or local anaesthesia and a sedative are needed. The operation itself requires a corneal surgeon with a supporting team. It can be performed in an inpatient setting or in an outpatient facility [17].

B0008. What kind of special premises are needed to use intrastromal corneal implants and the comparators?

B0009. What supplies are needed to use intrastromal corneal implants and the comparators?

For intrastromal corneal implants as well as corneal transplantation a sterile operation theatre is suggested [17,30].

In addition, for the implantation of intrastromal corneal implants, a channel has to be created to insert the device. This can be done with a femtosecond laser or mechanically; thus, several instruments are needed for the intervention (e.g., a Sinsky hook, a knife, etc.) [25].

CXL procedure mainly requires UVA light source and commercially available riboflavin. A bandage contact lens may be inserted at the end of the procedure. Topical steroid and nonsteroidal anti-inflammatory drops are commonly used during the postoperative period [5,6,29].

Several instruments are likewise required for corneal transplantation, as is a transplant from an adequate donor (requiring a donor management system, immunosuppressive drugs, etc.) [22].

Disscusion

Until the beginning of the new millennium, the treatment paradigm for keratoconus was essentially a simple 2-option process: (1) if the keratoconus was stable or exhibited minimal progression, with good best-corrected visual acuity (BCVA), the subject would be managed by spectacle or rigid gas-permeable contact lenses, (2) if the keratoconus was advanced or associated with scarring or reduced BCVA, the subject would be offered PK, and possible subsequent visual correction by contact lenses. However, there has been an explosion in options for treating keratoconus in the past 20 years, and such treatment plans are now outdated [9,32].

The treatment of keratoconus involves two important goals: improving vision and stopping the progression of disease; however no single treatment modality alone has been able to completely satisfy both of these goals [32]. Nevertheless, intrastromal corneal ring segments have become a mainstay in the treatment of corneal ectasia, particularly keratoconus. The concept behind ICRS insertion in keratectasia is not to eliminate the ectatic process, but to modify the corneal shape without removing tissue or manipulating the central cornea. The goal of this treatment is to improve visual acuity or

contact lens tolerance, thus delaying or eliminating the need for a corneal transplant; the surgery is less invasive and the results are generally reversible [24,29,32].

Even when most authors have reported good results in terms of improvement in visual acuity, a recently performed multicentric study found that the efficacy of ICRS implantation was related to the visual limitation of the patients at the time of surgery. It was observed that patients with good visual function at the time of surgery were more prone to lose lines of vision after the procedure. On the other hand, those cases with severe visual impairment before the procedure were the ones that benefited the most from ICRS implantation. These findings led to consider that ICRS implantation in cases with keratoconus and good vision should be undertaken with extreme caution and planned carefully because of the risk of losing vision in this group of patients [24,26].

Also, there has been particular interest in the newer treatment modalities as they offer the potential to treat the disease at an earlier stage, prevent the morbidity associated with disease progression, and preclude the need for the more invasive keratoplasty procedure. Since the clinical data after ICRS implantation do not indicate stopping disease progression, in terms of surgical approach, corneal cross-linking may prevent. Interestingly, the published evidence base that supports the use of CXL in keratoconus, although extensive, is not of as high quality as one might expect [9,23,24].

In addition, there are some reports published in the scientific literature that have shown that a combination of ICRS and CXL improves the vision and the refraction of patients with keratoconus. Moreover, there are some investigations reporting that a combination of ICRS together with CXL leads to more flattening of the cornea and reduction of the corneal cylinder than those cases treated with ICRS alone. Collagen crosslinking can be performed before, during, or after ICRS implantation, but the ideal sequence and timing of combined treatment is still uncertain [24,26].

So what does the future hold? It is evident that further progress in the field of keratectasia management will occur only with a better understanding of the basic pathophysiology of the disease process and the exact biomechanical response following CXL and ICRS implantation. Corneal hysteresis, elastography, waveform analysis, noncontact tonometry, multiphoton fluorescence, photon microscopy, and inverse computational analysis studies may well lead to new discoveries in this rapidly evolving field [24].

SAFETY

Research questions [1]

ID	Question
C0008	How safe are intrastromal corneal implants in relation to the comparators?
C0002	Are the harms related to dosage or frequency of applying intrastromal corneal implants?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the intrastromal corneal implants?
C0007	Are intrastromal corneal implants and other comparators associated with user-dependent harms?

The following *crucial* outcomes were used as evidence to derive a recommendation:

- intra-operative adverse events
- post-operative adverse events.

Intra-operative adverse events are those complications that occur during the surgical procedure: during the ring implantation or during the corneal transplantation. Post-operative adverse events are those complications that occur after the surgical intervention: e.g., ring movement or infections after corneal transplantation.

Patient safety

C0008. How safe are intrastromal corneal implants in relation to the comparators?

No studies were identified that are directly comparing the implantation of intrastromal corneal implants with corneal transplantation (e.g., keratoplasty) or no intervention for the treatment of keratoconus.

However, 1 prospective randomized study [5] was identified, which compared the intervention group of patients that underwent the implantation of intrastromal corneal rings (Keraring) with the control group of patients who also had the implantation of intrastromal corneal rings (Keraring) but one month later transepitheliail corneal cross-linking (TE-CXL) was performed as well. Extrusion of Kerarings occurred in 1 eye because of implant erosion. Unfortunately, the case was excluded from the study and it is unknown which group of patients experienced this complication.

In the single-arm studies, general adverse events occurred in 7 to 16% of the eyes [33,34,35,36]. Intra-operative adverse events, like difficulties in forming the intrastromal tunnel to implant the rings or anterior perforation, occurred in 0–2% of the eyes [33,34,35,36]. Post-operative adverse events occurred in 2 to 23% of the treated eyes [33,34,35,36,37], e.g., extrusion or migration of a segment, external infection or corneal perforation.

C0002. Are the harms related to dosage or frequency of applying intrastromal corneal implants?

Naturally, since the implantation of intracorneal rings is performed only once, the question is not relevant.

C0004. How does the frequency or severity of harms change over time or in different settings?

No direct evidence was found to answer this research question in an appropriate way.

However, it seems likely that the frequency and/or severity of harms slightly increase over time. The identified study with the longest duration and the most patients is the only one that shows the number of post-operative events per year of follow-up [37]. In Figure 1, the number and the percentage of post-operative events (per number of patients in the study) per year are shown.

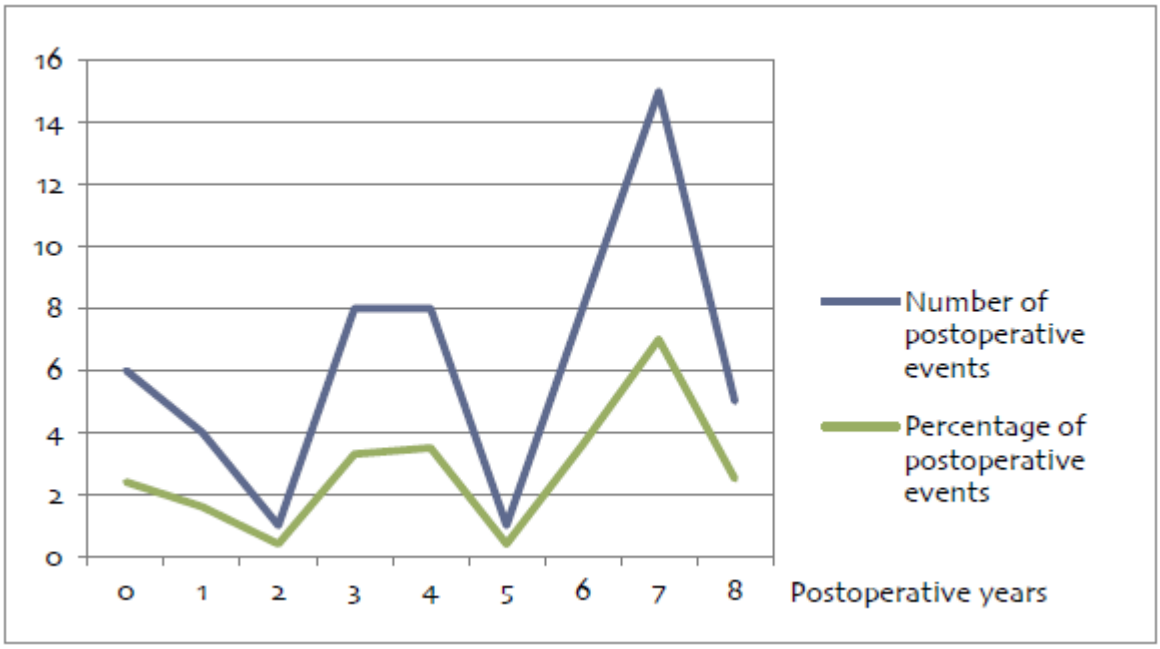

Figure 1. Number and percentage of post-operative events.

C0005. What are the susceptible patient groups that are more likely to be harmed through the use of the intrastromal corneal implants?

No direct evidence was found to answer this research question.

C0007. Are intrastromal corneal implants and other comparators associated with user-dependent harms?

No direct evidence was found to answer this research question. However, in all included studies intrastromal corneal implants were implanted by experienced eye surgeons [5,33,34,35,36,37].

Discussion

In general, keratoconus reduces corneal sensitivity, related to nerve fiber disruption from progressive ectasia as well as prolonged contact lenses wear. Besides having a relatively neurotrophic cornea, many patients with advanced keratoconus have other ocular surface problems as well. Penetrating keratoplasty and deep anterior lamellar keratoplasty tend to worsen any existing ocular surface problems, as both involve surface incisions, severing of corneal nerves, and placement of long-

lasting sutures. These difficulties are evidenced by chronic, punctate epithelial erosions which may persist indefinitely in 10–20% of eyes after PK [31].

Treatment for keratoconus has trended away from PK – and to some extent, even DALK – largely because of the problems these surgeries entail: ocular surface and wound healing difficulties, suture related issues, allograft reactions, glaucoma, and others. Mostly CXL and ICRS represent the second wave of therapeutic options for keratoconus, notable especially for being much less invasive, and therefore, potentially safer [31].

The ring segments can be implanted using mechanical or femtosecond laser-assisted techniques. The mechanical tunnel creation is more complex and dependent on the surgeon's skill, whereas the femtosecond laser-assisted tunnel technique is faster and more precise and hence has better reproducibility. Although rare, intraoperative complications have been described when performing the channels with the manual technique [26,29]. In general, mechanical tunnel creation may be associated with higher rates of complications compared with using femtosecond laser tunnel creation. Also, ICRS implantation in eyes with advanced keratoconus also was associated with more complications [29]. Visual symptoms such glare, halos, photophobia, and night vision problem is reported. Most complications of intrastromal ring implantation can be reversed by removing the segment, but serious complications can occur, such as intraoperative corneal perforation, infectious keratitis (corneal infection), damage to the central visual axis, or cornealmelt [4].

Although the strength of evidence for safety from included studies was low to very low, a treatment of keratoconus (and post-LASIK ectasia) with intrastromal corneal implants does not seem to be related with major adverse events. The rate of intra-operative adverse events seems to be low. However, the rate of post-operative adverse events was high in several studies.

Finally, a treatment of keratoconus as well as post-LASIK corneal ectasia with intrastromal corneal implants seems relatively safe – at least within a short time horizon. Additionally, all explantations or adjustments of intrastromal corneal implants due to adverse events were without any complications.

CXL procedure is related to some other issues. The most commonly performed and likely optimal protocol for CXL requires complete epithelial debridement. Subsequent UV radiation damages the underlying sub-epithelial nerve plexus. Consequently, any existing neurotrophic tendencies may worsen until nerve regeneration occurs and sensation is restored, a process that can require up to a year. This combined with post-operative soft contact lens wear dramatically raises the risk for infectious keratitis and stromal melting, particularly when concomitant ocular surface disease impairs normal corneal re-epithelialization [29,31]. Postoperative pain and risk of complications that result from epithelial debridement in the standard CXL procedure lead to the concept of CXL without epithelial debridement, which is termed as transepithelial CXL. As riboflavin does not readily penetrate the intact epithelium, enhanced riboflavin solutions or anesthetic eye drops containing compounds such as benzalkonium chloride that loosen the tight junctions of corneal epithelial cells are used in transepithelial CXL to obtain an effect comparable to the standard CXL with epithelial debridement; transepithelial CXL is less painful than standard epithelium-off CXL [29].

CLINICAL EFFECTIVENESS

Research questions [1]

ID	Question
D0001	What is the expected beneficial effect of intrastromal corneal implants on mortality?
D0005	How do intrastromal corneal implants affect symptoms and findings (severity, frequency) of keratoconus or post-LASIK corneal ectasia?
D0006	How do intrastromal corneal implants affect progression (or recurrence) of keratoconus or post-LASIK corneal ectasia?
D0011	What is the effect of intrastromal corneal implants on patients' body functions?
D0016	How does the use of intrastromal corneal implants affect activities of daily living?
D0012	What is the effect of intrastromal corneal implants on generic health-related quality of life?
D0013	What is the effect of intrastromal corneal implants on disease-specific quality of life?
D0017	Were patients satisfied with the technology?

The following *crucial* outcomes were used as evidence to derive a recommendation:

- Length of hospital stay (or time to resume work/normal activities)
- Re-operation rate
- Change of visual acuity (change of two or more Snellen lines)

The implantation of intrastromal corneal implants is supposed to be less invasive than corneal transplantation. Therefore, the length of hospital stay, 3 (or time to resume work or normal activities) after the intervention, was chosen as a crucial outcome.

The re-operation rate (including explantations) is the rate of how frequently patients had to be operated again, e.g., due to complications. This outcome is an indicator of the "life-expectancy" of the implants and transplants.

The change of visual acuity can be measured, for example, by uncorrected visual acuity (UCVA) or best-corrected visual acuity (BCVA) on the Snellen chart. An improvement or worsening of two and more Snellen lines can be considered as clinically relevant. Furthermore, the percentage of patients or eyes with improved (or worsened) visual acuity (two or more Snellen lines) has been defined as more relevant than the mean increase in visual acuity [19]. Therefore, only those studies where it was possible to cull this information from were considered.

Besides the three crucial outcomes, two additional outcomes were used to answer efficacy-related outcomes: quality of life and patient satisfaction.

Mortality

D0001. What is the expected beneficial effect of intrastromal corneal implants on mortality?

Mortality is not a relevant outcome for assessing the clinical effectiveness of intrastromal corneal implants, since neither the disease nor the intervention is life-threatening.

Morbidity

D0005. How do intrastromal corneal implants affect symptoms and findings (severity, frequency) of keratoconus or post-LASIK corneal ectasia?

Answering this research question was based on the outcome "change of visual acuity". Due to a lack of controlled trials, the effect on visual acuity of intrastromal corneal implants for a treatment of keratoconus cannot be compared with corneal transplantation, but will be based on uncontrolled data.

The change of visual acuity of *one and more Snellen lines* was reported in four single-arm studies. After 12 months, UCVA was improved in around 70–80% of eyes and worsened in less than 10% of eyes [35,36]. After 24 months, UCVA improved in 81% and worsened in 5% of treated eyes [36]. Similarly, BCVA improved in approximately 60–85% and worsened in 4–12% of the treated eyes (after 24 months: 68% improved, 15% worsened) [35,36]. Moreover, the improvement of UCVA and BCVA was considered statistically significant after six 6 and 12 months of implantation in one study [36].

The change of visual acuity of *two or more Snellen* lines after treatment, which has been defined as clinically relevant, has been reported in one single-arm study for UCVA [33] and in two single-arm studies for BCVA [33,34]: Six months after implantation, UCVA improved in 79% and worsened in none of the treated eyes [21]. In addition, BCVA rather improved in more eyes than worsened [33,34]: For example, after 6 months of implantation BCVA improved in 39–62% and worsened in 6–12% of eyes [33,34]. After 12 months of implantation, BCVA improved in 42% and worsened in 8% of the eyes that received an implant [34]. The improvement of UCVA and BCVA after six months of implantation compared to baseline was considered as statistically significant in one study [33].

The change of visual acuity was reported in RCT [5], where the intervention group of patients that underwent the implantation of intrastromal corneal rings (Kerarings) for the treatment of grades II–III of keratoconus was compared with the control group of patients who also had the implantation of intrastromal corneal rings (Keraring) for the treatment of grades II–III of keratoconus and one month later the corneal transepithelial collagen cross-linking was performed. There was a statistically significant improvement in the final UCVA from the preoperative values in both groups ($p<0.001$ and $p<0.001$, respectively). Median preoperative, 3 month postoperative and 6 month postoperative values of UCVA in intervention group were 0.05, 0.2 and 0.2, respectively; in control group these values were 0.05, 0.3, and 0.3, respectively. There was a statistically significant improvement in the final BCVA from the preoperative values in both groups ($p<0.001$ and $p<0.001$, respectively) [5]. Median preoperative, 3 month postoperative and 6 month postoperative values of BCVA in intervention group were 0.25, 0.3 and 0.4, respectively; in control group these values were 0.25, 0.5, and 0.5, respectively [5]. However, there was no statistically significant difference between groups regarding the UCVA improvement ($p=0.2$) and regarding the improvement in BCVA ($p=0.2$) [5].

D0006. How do intrastromal corneal implants affect progression (or recurrence) of keratoconus or post-LASIK corneal ectasia?

To answer this research question the outcome "re-operation rate" was used to (indirectly) measure the progression (or recurrence) of the disease. Thus, the higher the re-operation rate, the lower the chance of stopping or slowing the progression.

However, due to a lack of controlled trials, the effect on the re-operation rate of intrastromal corneal implants for a treatment of keratoconus cannot be compared with corneal transplantation, but will be based on uncontrolled data.

According to the available data, between 4 and 23% of the eyes with an implanted intrastromal corneal ring had to be re-operated [33,34,36,37].

Function

D0011. What is the effect of intrastromal corneal implants on patients' body functions?

Keratoconus and the treatment with intrastromal corneal implants exclusively affect the eyes and not the whole body. Thus, answering this research questions has been defined as not relevant.

The effect on visual acuity (the only affected body function) has already been addressed in the previous section (question D0005).

D0016. How does the use of intrastromal corneal implants affect activities of daily living?

Answering this research question was based on the outcome "length of hospital stay (or time to resume work/normal activities)". The outcome was not reported in any of the identified studies.

Health-related quality of life

D0012. What is the effect of intrastromal corneal implants on generic health-related quality of life?

No evidence was found to answer this research question (no identified study reported generic health-related quality of life).

D0013. What is the effect of intrastromal corneal implants on disease-specific quality of life?

To answer this research question the outcome "vision-related quality of life" was used. Due to a lack of controlled trials, the effect on quality of health of intrastromal corneal implants for a treatment of keratoconus cannot be compared with corneal transplantation, but will be based on uncontrolled data.

Vision-related quality of life was reported in two single-arm studies [33,34]. In one study, vision-related quality of life improved in 88.5% and worsened in 11.5% of patients, measured with the Visual Function-7 score (no information on this questionnaire was presented) [34]. In another study, the quality of vision was measured with the characteristics "poor", "fair", "good" and "excellent" by asking the patients [33]. Before implantation, 70% of patients had a "poor", and none had an "excellent" quality of vision. At 6 months after implantation, 24% of patients had "poor" and 9% of patients had "excellent" quality of vision [33].

Patient satisfaction

D0017. Were patients satisfied with the technology?

Due to a lack of controlled trials, the effect on patient satisfaction of intrastromal corneal implants for a treatment of keratoconus cannot be compared with corneal transplantation, but will be based on uncontrolled data.

The "patient satisfaction" outcome was reported in one of the identified single-arm studies as the change of self-reported satisfaction with vision [34]. According to that study, 73% of patients

reported an improvement in satisfaction and 8% reported a worsening of satisfaction with their vision [34].

Discussion

The aim of this report was to assess the clinical effectiveness and safety of a treatment of keratoconus or post-LASIK ectasia with intrastromal corneal rings (or ring segments) compared to corneal transplantations (or no intervention) [19].

Considering the findings of the included single-arm studies regarding clinical effectiveness, it seems that the implantation of intrastromal corneal implants can improve visual acuity in a clinically relevant manner (two or more Snellen lines). The uncorrected visual acuity improved two or more Snellen lines in approx. 80% of the eyes and the best-corrected visual acuity improved two or more Snellen lines in approx. 40–60% of the eyes during 6 to 12 months of follow-up [19,33,34].

However, there were also several cases with worsened visual acuity after a treatment with intrastromal corneal implants: worsened best-corrected visual acuity (two and more Snellen lines) in 6–12% of the eyes during follow-up [19,33,34].

In addition to improving visual acuity and refraction, it is thought that treatment with ICRS for keratoconus may add stability to the ectatic cornea, possibly halting or slowing the progression of the disease [32]. However, this procedure has its own limitations. Firstly, it does not affect the underlying biochemical properties of the cornea. Secondly, there is a limit to how much corneal flattening can be achieved [4].

The various management options alone or in combination have been proposed to delay or even prevent the need for corneal transplantation for keratoconus and have been successful in reducing the refractive error or flattening the cornea (ICRS), stabilizing the progression (CXL) of the disease, reducing the surface irregularity (PRK) and in cases of advanced cases helping in visual rehabilitation (DALK/PKP/FEK) [6,10,29].

ICRS may be successfully combined with other therapeutic approaches, such as CXL or PRK, in order to improve the visual, refractive and keratometric parameters in patients with keratoconus. CXL can be performed before, during, or after ICRS implantation [24]. Nevertheless, the sequence of the treatments or whether to perform them together in the same surgical session is still a topic of controversy [26,29,32]. Fortunately, the increasing complexity of ICRS treatment has brought with it promising results that have increasingly allowed keratoconus patient to achieve both improved vision and slowed progression of disease [32].

However, there seems to be a lack of published data on selecting the best treatment modality for a particular stage of keratoconus [6,29]. Nevertheless, due to a lack of controlled trials we are not able to draw any conclusions on the clinical effectiveness of intrastromal corneal implants for a treatment of keratoconus or post-LASIK ectasia compared to corneal transplantation or even no intervention [19].

CONCLUSIONS

1. Both keratoconus and post-LASIK corneal ectasia are rare disorders (prevalence <2 per 10,000 people) and often occurs during teenage years (median age of 25 years). Cause of corneal ectasia is probably related to a combination of an intrinsic predisposition to ectasia and an additional anatomical destabilising effect from the refractive surgery.

2. In total, five products of intrastromal corneal implants received market authorisation in Europe (CE marking). However, only four types are available: Ferrara RingTM (AJL OPHTHALMIC S.A., Spain); Intacs® and Intacs® SK (AJL OPHTHALMIC S.A., Spain); Keraring-Intrastromal corneal ring (Mediphacos, Brazil); MyoRing® (DIOPTEX, Austria). It seems very likely that the first generation implants Bisantis Segments (Optikon 2000 SpA and Soleko SpA, Italy) are not available anymore. The main difference between these products is their design (full rings or segments) with different shapes, diameters and thicknesses. Only MyoRing® is a full ring.

3. In the single-arm studies, general adverse events occurred in 7 to 16% of the eyes. Intra-operative adverse events, like difficulties in forming the intrastromal tunnel to implant the rings or anterior perforation, occurred in 0–2% of the eyes. Post-operative adverse events occurred in 2 to 23% of the treated eyes e.g., extrusion or migration of a segment, external infection or corneal perforation.

4. Re-operation rate varies between 4% and 23% of the eyes with implanted intrastromal corneal ring/ ring segments. Thus, the higher the re-operation rate, the lower the chance of stopping or slowing the progression. However, the main expected advantage of intrastromal corneal implants over other surgical interventions like corneal transplantation is that the implants can be removed relatively easily.

5. The comparison before and after the ring implantation have shown that the visual acuity has improved in a large proportion of patients: uncorrected visual acuity after 12 months was improved in 70–80% of eyes and worsened in less than 10%; after 24 months, improved in 81% and worsened in 5% of treated eyes. Similarly, best corrected visual acuity after 12 months improved in 60–85% and worsened in 4–12% of the treated eyes; after 24 months, improved in 68% and worsened in 15% worsened of the treated eyes. Vision-related quality of life improved in 88.5% and worsened in 11.5% of patients. Also, 73% of patients reported an improvement in satisfaction and 8% reported a worsening of satisfaction with their vision.

RECOMMENDATIONS

1. The current evidence is not sufficient to prove that intrastromal corneal implants are equally or more effective and safe than corneal transplantation or no intervention for a treatment of keratoconus or post-LASIK corneal ectasia. However, the comparison before and after the ring implantations of the single-arm studies have shown that the visual acuity has improved after implanting intrastromal corneal rings/ring segments and that improvement has been clinically relevant in a large proportion of patients.

2. Due to the minor invasivity and the reversibility, intrastromal corneal implants should be considered before corneal transplantation. Although, that is recommended with the following restrictions:
   - The patient has contact lens intolerance (or is not able to wear contact lenses anymore).
   - The individual indications and contra-indications for the use of the several products must be considered (e.g. adequate thickness of cornea).
   - The implantation of intrastromal corneal rings (or ring segments) should exclusively be offered in big centres, like medical universities.
   - The safety of intrastromal corneal implants for a treatment of keratoconus or post-LASIK corneal ectasia should be monitored and recorded in a national database. The data can be used to further adapt the recommendations for the use of intrastromal corneal implants.

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36. Colin J, Malet FJ. Intacs for the correction of keratoconus: two-year follow-up. Journal of Cataract & Refractive Surgery. 2007; 33(1):69-74.
37. Ferrer C. Causes of intrastromal corneal ring segment explantation: Clinicopathologic correlation analysis. Journal of Cataract & Refractive Surgery. 2010; 33:970-977.
38. EUnetHTA Joint Action 1, Work Package 5. HTA Adaptation Toolkit & Glossary. Adapting existing HTAs from one country into other settings version 5.0; 2011. Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/EUnetHTA_adptation_toolkit_2011%20version%205.pdf

APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCES USED

This health technology assessment ("Intrastromal corneal implants for ectatic corneal disorders") which was implemented by the LBI-HTA (Ludwig Boltzmann Institute-Health Technology Assessment, Austria) was updated and adapted for the context of Lithuania. The European Commission initiates and supports the usage and adaptation of EunetHTA's health technology assessments for national needs of the European countries.

A working version of the HTA Core Model® for Medical and Surgical Interventions (version 3.0) was used as the primary source for selecting the assessment elements. Additionally, assessment elements from other EUnetHTA Core Model Applications were screened and included, if believed relevant to the present assessment.

The systematic literature search was conducted with time limitation between 30th December 2014 and 21th June 2016, inclusive. Also, information for the assessment was updated and used from the LBI-HTA decision support document No. 85 ("Intrastromal corneal implants for ectatic corneal disorders").

The adaptation of the assessment was based primarily on a basic systematic literature search in the following sources:

- Cochrane Library database;
- PubMed (Medline);
- CRD database;
- Hand searches including articles from the manufacturers.

Relevant literature sources and articles for the adaptation for the 'Safety' and 'Clinical effectiveness' domains were selected by the VASPVT **(**State Health Care Accreditation Agency under the Ministry of Health, Lithuania). References were included or excluded according to the PICO scheme described in the summary.

Selection of relevant documents was performed by two independent researchers. If the same data were duplicated in multiple articles, only results from the most comprehensive or most recent article were included. Consensus was found in all cases about the inclusion and exclusion of individual studies.

The relevant information from the feasible studies was retrieved without any further analysis. For all studies the methodological quality was assessed using the IHE checklist for case series (see more in LBI-HTA decision support document No. 85 "Intrastromal corneal implants for ectatic corneal disorders") or the Cochrane risk of bias checklist for RCTs, by two review authors, independently from each other. For assessing the quality of SRs, the AMSTAR checklist for systematic reviews was used. The risk of bias analysis is shown in the Appendix 4.

Incidentally, a comparative analysis was not applicable, since we could not identify studies for every product and indication, except 1 RCT. Moreover, the quality of evidence did not allow any comparative analysis. LBI-HTA used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the quality of the evidence for 'Clinical effectiveness' and 'Safety'. Evidence tables of individual single-arm studies (5 studies) included for clinical effectiveness and safety can be found on LBI-HTA decision support document No. 85 "Intrastromal corneal implants for ectatic corneal disorders".

A manual search and basic search were performed for ‘Health problem and current use’ and ‘Description and technical characteristics’.

Most of the research questions will be answered in plain text format. In addition, evidence tables are used to show relevant information on the individual studies. The analysis is qualitative and not quantitative due to a lack of comparison groups and heterogeneity of the data.

Reporting of results

For evaluating safety- and efficacy-related outcomes we accepted RCTs, prospective non-randomized controlled trials and – in case we were unable to identify relevant controlled studies – single-arm studies with at least 50 eyes.

Information was used from the LBI-HTA (Ludwig Boltzmann Institute-Health Technology Assessment, Austria) decision support document No. 85 (“Intrastromal corneal implants for ectatic corneal disorders” [19], where five single-arm studies with a total of 627 eyes [19] assessing the safety and efficacy of intrastromal corneal implants for the treatment of keratoconus.

The mean age of patients differed between 26 and 37 years [5,19]. The minority of patients were females (30–50%) [19] with grades I to IV of keratoconus [5,19]. The follow-up of the studies was 6 months [5] 12 months [19], 24 months up to 96 months (8 years). The loss to follow-up rate differed between 18 and 76% [19].

Also, one randomized study with 40 eyes (29 patients) was identified comparing the intervention group of patients that underwent the implantation of intrastromal corneal rings (Kerarings) with the control group of patients who also had the implantation of intrastromal corneal rings (Keraring) but one month later corneal transepithelial collagen cross-linking (TE-CXL) was performed for the treatment of grades II-III of keratoconus [5]. The mean age of patients was 28 and 26.4 years in intervention and control groups respectively. The follow-up of the RCT was 6 months.

Intacs® were implanted in all studies [19] except RCT [5]. Furthermore, Keraring intracorneal ring segments were implanted in two studies [19].

The detailed study characteristics and results of the included studies are displayed in Appendix 3 included for clinical effectiveness and safety.

There were no studies assessing the safety and the clinical effectiveness of other products, like Ferrara Ring™, MyoRing® or probably Bisantis Segment for the treatment of keratoconus. In addition, there were no studies assessing the safety of intrastromal corneal implants for the treatment of post-LASIK corneal ectasia.

Length of hospital stay (or time to resume work/ normal activities) and reoperation rate were not considered for recommendation: Only a direct comparison with corneal transplantation would have been allowed to assess the clinical effectiveness of intrastromal corneal implants for a treatment of keratoconus and post-LASIK corneal ectasia.

Evidence tables of five single-arm studies included for clinical effectiveness and safety can be found in the LBI-HTA (Ludwig Boltzmann Institute-Health Technology Assessment, Austria) decision support document No. 85 (“Intrastromal corneal implants for ectatic corneal disorders” [19]. Evidence tables of RCT can be found in Appendix 3.

Quality assessment

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for every defined outcome parameter individually. Each study (except RCT) was rated by two independent researchers from LBI. All relevant study

results for each endpoint were thereby summarised and assessed regarding the strength of evidence. In case of disagreement, a third researcher was involved to solve the difference [19]. A detailed description of the used criteria for assessing the strength of evidence is stated in the internal manual of the LBI-HTA or in the recommendations of GRADE, respectively [19].

Overall, the strength of evidence for clinical effectiveness and the safety of intrastromal corneal implants for the treatment of keratoconus is low to very low. There was neither any evidence available to assess the efficacy, nor to assess the safety of intrastromal corneal implants for the treatment of post-LASIK corneal ectasia (compared to corneal transplantation or no intervention) that matched inclusion criteria [19].

One additional RCT, found during the adaptation process, was assessed by authors using the CONSORT 2010 checklist for RCT. The risk of bias was rated as high and a number of issues which affected the outcome data were identified. The RCT is affected by absence of patient blinding, attrition bias and reporting bias.

The quality assessment table of the selected five single-arm studies can be found in the LBI-HTA (Ludwig Boltzmann Institute-Health Technology Assessment, Austria) decision support document No. 85 ("Intrastromal corneal implants for ectatic corneal disorders" [19]. More detailed information on the RCT quality assessment can be found in Appendix 4.

Limitations

The aim of this report was to assess the clinical effectiveness and safety of a treatment of keratoconus or post-LASIK ectasia with intrastromal corneal rings (or ring segments) compared to corneal transplantations and corneal cross-linking (or no intervention).

Overall, there were no controlled trials available to assess the clinical effectiveness or safety of intrastromal corneal implants in comparison to corneal transplantations (or no intervention). However, 1 prospective randomized study comparing intrastromal corneal implants with intrastromal corneal implants plus corneal cros-linking was found. In total, we selected 5 single-arm studies with 627 eyes that met our inclusion criteria [33,34,35,36,37] and 1 RCT [5].

Unfortunately, it was decided to exclude all case series with less than 50 eyes. There were probably studies with less than 50 eyes with a longer follow-up or studies implanting other products (e.g., Ferrara Ring™ or MyoRing®).

Furthermore, it was decided to exclude all retrospective studies – even controlled studies with a retrospective control group where patients received a corneal transplantation – because sources of error due to confounding and bias are more common in retrospective studies than in prospective ones. Still, there were two studies included without precise information on whether they were conducted pro- or retrospectively [35,37].

One of the studies also included patients who had other diseases than keratoconus or post-LASIK corneal ectasia (e.g., myopia) [37]. Hence, this study was excluded although it included a large number of patients and had a long follow-up.

A major issue is that keratoconus and post-LASIK corneal ectasia are rare diseases with a low incidence, resulting in low patient numbers. There are even fewer patients who are contact lens intolerant and/or need a corneal transplantation (and are therefore eligible for implantation of intrastromal corneal rings). Therefore, it is difficult to conduct prospective controlled trials or randomised controlled trials for assessing the clinical effectiveness of intrastromal corneal implants compared to corneal transplantation or corneal cross-linking procedure (or no intervention). An additional issue for conducting controlled trials is that one study group needs an adequate donor for the corneal transplant and patients must wait for the transplantation. Although conducting RCTs of

intrastromal corneal implants versus corneal transplantation for keratoconus is difficult, it does not seem impossible [19].

ADAPTATION TOOLKIT

Table I. Speedy sifting questions [38]

Speedy sifting questions: Assessment of relevance	**Answers**
1. Are the policy and research questions being addressed relevant to your questions?	Yes.
2. What is the language of this HTA report? Is it possible to translate this report into your language?	Yes.
3. Is there a description of the health technology being assessed?	Yes; pages 7, 20.
4. Is the scope of the assessment specified?	Yes; page 15.
5. Has the report been externally reviewed?	Yes; page 2.
6. Is there any conflict of interest?	Yes; page 2.
7. When was the work that underpins this report done? Does this make it out of date for your purposes?	Yes; pages 2, 16, 58.
8. Have the methods of the assessment been described in the HTA report?	Yes; pages 7, 16, 41.

HTA available at: http://eprints.hta.lbg.ac.at/1055/1/DSD_85.pdf

Table II. Technology's use domain questions [38]

Questions	Answers
To assess relevance:	
1.What is the research question considered? Is the research question considered within this section of the report relevant to your question?	Yes; pages 7, 15.
To assess reliability:	
2. Were conditions, target group, relevant interventions or comparisons between interventions and relevant outcomes appropriately defined?	Yes; pages 15, 20, 26–29, 33, 38.
3. Is the information provided on technology use and development complete and comprehensive? Are the methods and sources used when elaborating the background information well documented?	Partly, update needed.
4. Are patterns of utilisation, diffusion, indications and time trends adequately described?	Partly, update needed.
5. Is an analysis of the regulatory status of the technology provided (market admission, status in other countries)?	Yes; pages 20, 22–23. Update needed.
To assess transferability:	
6. Is there any consideration of when and how technical characteristics affect outcomes?	Yes; pages 20, 21.
7. Are there any differences in the use of this technology within the target setting (compared to the uses described in the HTA report for adaptation)?	No.

Table III. Safety domain questions [38]

Questions	Answers
To assess relevance:	
1. Were harms or safety assessed?	Yes; page 39.
2. Is the scope of the safety assessment relevant to your question?	Yes; pages 15, 37.
To assess reliability:	
3. Was the search for studies reasonably comprehensive?	Yes; pages 16, 37–38, 58.
4. Were special sources consulted (disease registers, routinely data collected (on utilisation, costs, adverse effects, etc.), consumer associations, etc..)	Yes; page 37.
5. What are the sources of information/ data (e.g. surveillance databases, declaration of incidents, safety report, RCT, case reports)?	Yes; pages 16, 37.
6. Were the criteria used for deciding which studies to include in the HTA report reported?	Yes; pages 16, 38, 45.
7. Was bias in the selection of studies avoided?	Yes; pages 38, 54.
8. Did the selection of studies (in particular the choice of eligible study designs) minimise the possibility of including studies with a high propensity for bias?	Yes; pages 38, 54.
9. Were the criteria used for assessing the validity of the included studies reported?	Yes; page 54.

10. a) Were the inclusion criteria used for the primary studies appropriate to the study question posed by the HTA report? b) Were the criteria used to assess the validity of the primary study appropriate?	Yes; page 38. Yes; page 38.
11. Which risks have been reported and how were they measured?	Yes; page 56.
12. a) Were the study outcomes valid? b) Were the study outcomes pertinent?	Partly; page 39.
13. Are the number of patients, their representativeness and the quality of the data high enough to exclude a modest but clinically relevant rate of serious complications? I.e. what is the potential for overlooking a possible serious adverse event?	No; pages 39, 51–54.
14. Is there a possibility for a „class" effect adverse reaction or safety problem?	No.
To assess transferability:	
15. Does the population described for eligibility match the population to which it is targeted in the target setting?	Yes; pages 15, 39.
16. Are there any reasons to expect differences in complication rates (e.g. epidemiology, genetic issues, healthcare system (quality of care, surveillance))?	Yes; page 39.
17. Are the requirements for its use (special measures needed for use/ implementation, maintenance, etc.) available in the target setting?	Yes; page 21.
18. Is the necessary expertise (knowledge and skills) available in the target setting?	Yes; page 21.
19. a) Is safety particularly dependent on training? b) Are there types of teams to which the procedure should be limited for safety reasons? c) Is there a need for special training or certification to deliver the intervention properly? d) Would it be possible (affordable) to organise such training, if any?	Partly; page 21. Yes; page 22. Partly; pages21–22. No.

Table IV. Effectiveness domain questions [38]

Questions	**Answers**
To assess relevance:	
1. a) What is the research question considered? b) Is the research question considered within this section of the HTA report relevant to your HTA question?	Yes; pages 15, 31.
2. Are the outcome measures relevant for your HTA question?	Yes; pages 15, 33.
3. Were the search methods used to find studies relevant to the main question(s) stated?	Yes; pages 16, 32, 58.
To assess reliability:	
4. Was the search for studies reasonably comprehensive?	Yes; pages 16, 33, 45.
5. Were the criteria used for deciding which studies to include in the HTA	Yes;

report reported?	pages 16, 33, 45.
6. Was bias in the selection of studies avoided?	Yes; pages 32, 54–56.
7. Did the selection of studies (in particular the choice of eligible study designs) minimise the possibility of including studies with a high propensity for bias?	Yes; pages 33, 57.
8. Were the criteria used for assessing the validity of the included studies reported?	Yes; page 54.
9. Was the validity of all studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analysing the studies that are cited)?	Yes; pages 33, 54.
10. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?	No.
11. Were the findings of the relevant studies combined appropriately with respect to the main question the HTA report addresses?	Yes; page 33.
12. Were the conclusions made by the authors supported by the data and/ or analysis reported in the HTA report?	Yes; pages 47–48.
13. How likely is it that the relevance of this HTA report has changed due to additional research that had started, completed or been published since this Health Technology Assessment report?	Unlikely.
To assess <u>transferability</u>:	
14. Would you expect the baseline risk of patients within your own setting to be the same as the baseline risk of those patients considered within the HTA report for adaptation? (assuming that patients receive the same treatment and same comparator).	Yes.

APPENDIX 2: DOCUMENTATION OF THE BASIC SEARCH STRATEGIES

Search strategies

Database: PubMed (MEDLINE)
Search date: 2016-06-21
Results: 79 hits.

	Searches	Results
1.	keratoconus	5388
2.	keratokonu*	37
3.	keratokoni*	7
4.	cornea* ectasia*	752
5.	iatrogenic cornea*	376
6.	Iatrogenic Disease	67305
7.	Corneal Diseases	51559
8.	(Iatrogenic Disease) AND (Corneal Diseases)	292
9.	keratectasia*	208
10.	((keratoconus) OR (keratokonu*) OR (keratokoni*) OR (cornea* ectasia*) OR (iatrogenic cornea*) OR ((Iatrogenic Disease) AND (Corneal Diseases)) OR (keratectasia*))	6231
11.	(intracornea* OR intra-cornea* OR intrastroma* OR intra-stroma*)	1717
12.	ICRS	717
13.	((cornea* implant) OR (cornea* implantat*))	6546
14.	((intracornea* OR intra-cornea* OR intrastroma* OR intra-stroma*) OR (ICRS) OR ((cornea* implant) OR (cornea* implantat*)))	8267
15.	((keratoconus) OR (keratokonu*) OR (keratokoni*) OR (cornea* ectasia*) OR (iatrogenic cornea*) OR ((Iatrogenic Disease) AND (Corneal Diseases)) OR (keratectasia*)) AND ((intracornea* OR intra-cornea* OR intrastroma* OR intra-stroma*) OR (ICRS) OR ((cornea* implant) OR (cornea* implantat*)))	599
16.	((keratoconus) OR (keratokonu*) OR (keratokoni*) OR (cornea* ectasia*) OR (iatrogenic cornea*) OR ((Iatrogenic Disease) AND (Corneal Diseases)) OR (keratectasia*)) AND ((intracornea* OR intra-cornea* OR intrastroma* OR intra-stroma*) OR (ICRS) OR ((cornea* implant) OR (cornea* implantat*))) Filters: Publication date from 2014/12/30 to 2016/06/21.	88
17.	((keratoconus) OR (keratokonu*) OR (keratokoni*) OR (cornea* ectasia*) OR (iatrogenic cornea*) OR ((Iatrogenic Disease) AND (Corneal Diseases)) OR (keratectasia*)) AND ((intracornea* OR intra-cornea* OR intrastroma* OR intra-stroma*) OR (ICRS) OR ((cornea* implant) OR (cornea* implantat*))) Filters: Publication date from 2014/12/30 to 2016/06/21, English.	79

Database: Cochrane Library
Search date: 2016-06-21
Results: 5 hits.

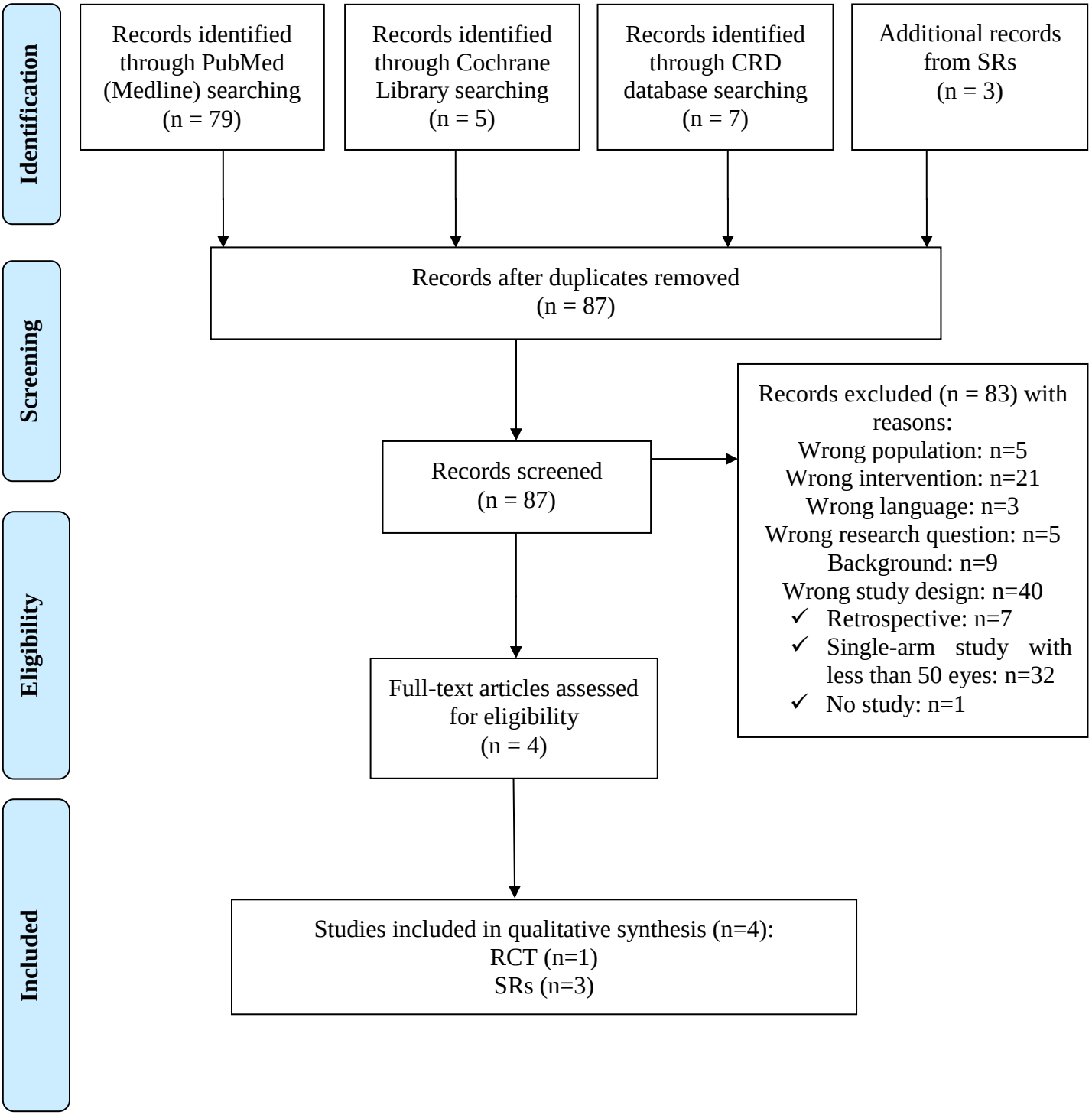
	Searches	Results
1.	MeSH descriptor: [Keratoconus] explode all trees	119
2.	keratoconu*	264
3.	keratoconi*	38
4.	cornea* NEAR ectasia*	27
5.	iatrogenic cornea*	15
6.	MeSH descriptor: [Iatrogenic Disease] explode all trees	1342
7.	MeSH descriptor: [Corneal Diseases] explode all trees	1171
8.	#6 AND #7	1
9.	keratectasia*	5
10.	#1 OR #2 OR #3 OR #4 OR #5 OR #8 OR #9	290
11.	(intracornea* OR intra-cornea* OR intrastroma* OR intra-stroma*) NEAR ring*	52
12.	ICRS	59
13.	cornea* NEAR implant*	284
14.	#11 OR #12 OR #13	343
15.	#10 AND #14	32
16.	#10 AND #15 Publication Year from 2015 to 2016	5

Database: CRD database
Search date: 2016-06-21
Results: 0 hits.

	Searches	Results
1.	MeSH DESCRIPTOR keratoconus EXPLODE ALL TREES	19
2.	(keratocon*)	30
3.	(cornea* NEAR ectasia*)	2
4.	(iatrogeniccornea*)	0
5.	(keratectasia*)	0
6.	#1 OR #2 OR #3	31
7.	(#1 OR #2 OR #3) WHERE LPD FROM 30/12/2014 TO 21/06/2016	7

Flow charts of study selection

Table V. Flow chart showing selection of studies.



Questions used from HTA Core Model Application for Medical and Surgical Interventions (version 3.0)

Health problem and current use of the technology:

ID	Question
A0001	For which health conditions, and for what purposes is intrastromal corneal implants used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for keratoconus or post-LASIK corneal ectasia?
A0004	What is the natural course of keratoconus or post-LASIK corneal ectasia?
A0005	What is the burden of keratoconus or post-LASIK corneal ectasia?
A0006	What are the consequences of keratoconus or post-LASIK corneal ectasia for society?
A0024	How is keratoconus or post-LASIK corneal ectasia currently diagnosed according to published guidelines and in practice?
A0025	How is keratoconus or post-LASIK corneal ectasia currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is intrastromal corneal implants utilised?
A0020	For which indications have intrastromal corneal implants received marketing authorisation or CE marking?
A0021	What is the reimbursement status of intrastromal corneal implants?

Description and technical characteristics of technology

ID	Question
B0001	What are intrastromal corneal implants and the comparators?
B0002	What is the claimed benefit of intrastromal corneal implants in relation to the comparators?
B0003	What is the phase of development and implementation of intrastromal corneal implants and the comparators?
B0004	Who administers intrastromal corneal implants and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use intrastromal corneal implants and the comparators?
B0009	What supplies are needed to use intrastromal corneal implants and the comparators?
B0010	What kind of data/records and/or registry are needed to monitor the use of intrastromal corneal implants and corneal transplantation (or no intervention)?

Safety

ID	Question
C0008	How safe are intrastromal corneal implants in relation to the comparators?
C0002	Are the harms related to dosage or frequency of applying intrastromal corneal implants?

C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the intrastromal corneal implants?
C0007	Are intrastromal corneal implants and other comparators associated with user-dependent harms?

Clinical effectiveness

ID	Question
D0001	What is the expected beneficial effect of intrastromal corneal implants on mortality?
D0005	How do intrastromal corneal implants affect symptoms and findings (severity, frequency) of keratoconus or post-LASIK corneal ectasia?
D0006	How do intrastromal corneal implants affect progression (or recurrence) of keratoconus or post-LASIK corneal ectasia?
D0011	What is the effect of intrastromal corneal implants on patients' body functions?
D0016	How does the use of intrastromal corneal implants affect activities of daily living?
D0012	What is the effect of intrastromal corneal implants on generic health-related quality of life?
D0013	What is the effect of intrastromal corneal implants on disease-specific quality of life?
D0017	Were patients satisfied with the technology?

APPENDIX 3: DESCRIPTION OF THE EVIDENCE USED

Evidence tables of individual studies included

Table VI. Evidence table for randomized controlled trial study details.

Study details				Population, procedure details and follow-up								
Author, Years [ref.]	**Country**	**Study design**	**CoI SoF**	**Intervention/ Product Comparator**	**N. of eyes/ pts.**	**Age of pts. (yrs.)**	**Sex (% female)**	**Clinical classification**	**Primary endpoint(s)**	**Inclusion criteria**	**Follow -up (mo.)**	**Loss to follow-up, n (%) of eyes**
Elsaftawy, 2015 [5]	Egypt	Randomized comparative case series, prospective.	**CoI:** None. **SoF:** None.	**A:** ICRS (Keraring), topical anesthetics, manual tunnel creation.	**Total: 40/29** **A:** 20/NA	**A:**Ø 28.0 (SD 4.8)	NA	**A:** Grade II–III	**A:** Improvement of UCVA**, maintenance of CDVA, BCVA, refraction and topographical profile values, post-operative complications.	**A:** Progressive keratoconus, contact lens intolerance, clear cornea. Corneal thickness ≥400 µm; BCVA >10/100; absence of any other ocular or systemic diseases.	**A:** 6	NA
				B: ICRS (Keraring), topical anesthetics, manual tunnel creation. + 1 mo. later TE-CXL (ParaCel), topical anesthetics, UVA irradiation (370nm).	**B:** 20/NA	**B:**Ø 26.4 (SD 5.3)		**B:** Grade II–III	**B:** Improvement of UCVA**, maintenance of CDVA, BCVA, refraction and topographical profile values, post-operative complications.	**B:** Progressive keratoconus, contact lens intolerance, clear cornea. Corneal thickness ≥400 µm. BCVA >10/100; absence of any other ocular or systemic diseases.	**B:** 6	

Legend: % – percents; µm – micrometer; BCVA – best-corrected visual acuity; CDVA – corrected distance visual acuity; CoI – conlict of interests; ICRS – intracorneal ring segments; mo. – months; n – number; NA – not applicable; nm – nanometers; Ø – mean; pts. – patients; ref. – reference; SoF – source of funding; TE-CXL – transepithelial corneal collagen cross-linking; UCVA – uncorrected visual acuity; UVA – ultraviolet A; yrs. – years.

** – UCVA and UDVA (uncorrected distance visual acuity) has the same meaning. However, in RCT uncorrected visual acuity was defined as UDVA, but in order to unify the definition with the one which was used in other 5 single-arm studies, we choose to use UCVA.

Table VII. Evidence table for randomized controlled study outcomes.

Author, Years [ref.]	Intervention/ Product Comparator	Efficacy-related outcomes					Safety-related outcomes		
		Length of hospital stay/ time to work resumption in days	Re-operation rate in % (n) eyes	Change of visual acuity (Med. (IQR))	Quality of life (health- or vision-related)	Patient satisfaction	Adverse events, general in % (n) eyes	Adverse events, intra-operative in % (n) eyes	Adverse events, post-operative in % (n) eyes
Elsaftawy, 2015 [5]	**A:** ICRS (Keraring), topical anesthetics, manual tunnel creation.	NA	NA	**A:** **UCVA****: Baseline: 0.05 (0.04, 0.10) Aft. 1 mo.: 0.2 (0.1, 0.3)* Aft. 3 mo.: 0.2 (0.1, 0.4)* Aft. 6 mo.: 0.2 (0.1, 0.4)* p <0.001 **BCVA**: Baseline: 0.25 (0.10, 0.50) Aft. 1 mo.: 0.3 (0.3, 0.6)* Aft. 3 mo.: 0.3 (0.3, 0.6)* Aft. 6 mo.: 0.4 (0.3, 0.7)*ǂ p <0.001	NA	NA	NA	NA	NA
	B: ICRS (Keraring), topical anesthetics, manual tunnel creation. + 1 mo. later TE-CXL (ParaCel), topical anesthetics, UVA irradiation (370nm).			**B:** **UCVA**:** Baseline: 0.05 (0.05, 0.10) 1 mo. bf. TE-CXL: 0.3 (0.1, 0.4)* 1 mo. aft. TE-CXL: 0.3 (0.2, 0.4)* Aft. 3 mo.: 0.3 (0.2, 0.5)* Aft. 6 mo.: 0.3 (0.2, 0.5)* p <0.001 **BCVA:** Baseline: 0.25 (0.10, 0.38) 1 mo. bf. CXL: 0.4 (0.3, 0.5)* 1 mo. aft. CXL: 0.5 (0.3, 0.6)*ǂ Aft. 3 mo.: 0.5 (0.4, 0.6)* Aft. 6 mo.: 0.5 (0.4, 0.7)* p <0.001					

Legend: % – percents; µm – micrometer; aft – after; BCVA – best-corrected visual acuity; bf. – before; ICRS – intracorneal ring segments; IQR – interquartile range; Med. – median; mo. – months; n – number; NA – not applicable; nm – nanometers; ref. – reference; TE-CXL – transepithelial corneal collagen cross-linking; UDVA – uncorrected distance visual acuity; UVA – ultraviolet A; yrs. – years.

* Significant change compared with baseline measurements.

** – UCVA and UDVA (uncorrected distance visual acuity) has the same meaning. However, in RCT uncorrected visual acuity was defined as UDVA, but in order to unify the definition with the one which was used in other 5 single-arm studies, we choose to use UCVA.

ǂ Significant change compared with previous visit measurements.

APPENDIX 4: QUALITY ASSESSMENT OF SELECTED STUDIES

Included studies

RCT	
1.	Elsaftawy HS, Ahmed MH, Saif MY, Mousa R. Sequential Intracorneal Ring Segment Implantation and Corneal Transepithelial Collagen Cross-Linking in Keratoconus. Cornea. 2015 Nov;34(11):1420-6.
SRs	
1.	Fischer S, Zechmeister-Koss I, Charpentier E. Intrastromal corneal implants for ectatic corneal disorders. Decision Support Document No. 85; 2015. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.
2.	Mandathara PS, Stapleton FJ, Willcox MD. Outcome of Keratoconus Management: Review of the Past 20 Years' Contemporary Treatment Modalities. Eye Contact Lens. 2016 May 11.
3.	Ziaei M, Barsam A, Shamie N, Vroman D, Kim T, Donnenfeld ED, Holland EJ, Kanellopoulos J, Mah FS, Randleman JB, Daya S, Güell J. Reshaping procedures for the surgical management of corneal ectasia. J Cataract Refract Surg. 2015 Apr;41(4):842-72.

Excluded studies

Reference		**Exclusion criteria**
1.	Menga Mengarelli C, Pichon-Riviere A, Augustovski F, García Martí S, Alcaraz A, Bardach A, Ciapponi A, López A, Rey-Ares L. [Corneal collagen crosslinking with riboflavin for keratoconus patients]. 2015. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS).	Wrong language: Spanish.
2.	Macchiavello D, Augustovski F, Pichon-Riviere A, Garcķa Martķ S, Alcaraz A, Bardach A, Ciapponi A, López A, Rey-Ares L. Intracorneal rings for patients with keratoconus. 2015. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS).	Wrong language: Spanish.
3.	Haute Autorité de Santé. Corneal collagen cross-linking and intrastromal corneal ring segments in the treatment of corneal ectasia. 2015. Haute Autorité de Santé (French National Authority for Health) (HAS).	Wrong language: French.
4.	Sykakis E, Karim R, Evans JR, Bunce C, Amissah-Arthur KN, Patwary S, McDonnell PJ, Hamada S. Corneal collagen cross-linking for treating keratoconus. John Wiley & Sons, Ltd. 2015;3.	Background.
5.	Arribas-Pardo P, Mendez-Hernandez C, Cuiña-Sardiña R, Fernandez-Perez C, Diaz-Valle D, Garcia-Feijoo J. Measuring intraocular pressure after intrastromal corneal ring segment implantation with rebound tonometry and Goldmann applanation tonometry. Cornea. 2015 May;34(5):516-20.	Wrong research question.
6.	Poulsen DM, Kang JJ. Recent advances in the treatment of corneal ectasia with intrastromal corneal ring segments. Curr Opin Ophthalmol. 2015 Jul;26(4):273-7.	Background.
7.	Rapuano CJ. Prevention of Iatrogenic Keratectasia. Klin Monbl Augenheilkd. 2016 Jun;233(6):695-700.	Background.
8.	Daxer A. Biomechanics of Corneal Ring Implants. Cornea. 2015 Nov;34(11):1493-8.	Background.
9.	Mohammadpour M, Hahemi H, Jabbarvand M. Technique of simultaneous femtosecond laser assisted Myoring implantation and accelerated intrastromal collagen cross-linking for management of progressive keratoconus: A novel technique. Cont Lens Anterior Eye. 2016 Feb;39(1):9-14.	Wrong intervention.
10.	Lago MA, Rupérez MJ, Monserrat C, Martínez-Martínez F, Martínez-Sanchis S, Larra E, Díez-Ajenjo MA, Peris-Martínez C. Patient-specific simulation of the intrastromal ring segment implantation in corneas with keratoconus. J Mech Behav Biomed Mater. 2015 Nov;51:260-8.	Wrong research question.
11.	Antonios R, Dirani A, Fadlallah A, Chelala E, Hamadeh A, Jarade E. Acute Corneal Hydrops 3 Years after Intra-corneal Ring Segments and Corneal Collagen Cross-linking. Middle East Afr J Ophthalmol. 2016 Jan-Mar;23(1):156-9.	Wrong study design: single-arm study with less than 50 eyes.
12.	Elbaz U, Shen C, Lichtinger A, Zauberman NA, Goldich Y, Ziai S, Rootman DS. Accelerated versus standard corneal collagen crosslinking combined with same day phototherapeutic	Wrong intervention.

	keratectomy and single intrastromal ring segment implantation for keratoconus. Br J Ophthalmol. 2015 Feb;99(2):155-9.	
13.	Al-Tuwairqi WS, Osuagwu UL, Razzouk H, Ogbuehi KC.One-Year Clinical Outcomes of a Two-Step Surgical Management for Keratoconus-Topography-Guided Photorefractive Keratectomy/Cross-Linking After Intrastromal Corneal Ring Implantation. Eye Contact Lens. 2015 Nov;41(6):359-66.	Wrong intervention.
14.	Vega-Estrada A, Alió JL, Plaza-Puche AB. Keratoconus progression after intrastromal corneal ring segment implantation in young patients: Five-year follow-up. J Cataract Refract Surg. 2015 Jun;41(6):1145-52.	Wrong study design: single-arm study with less than 50 eyes.
15.	Puell MC, Carballo-Álvarez J. Forward light scatter and visual acuity before and after intrastromal corneal ring segment implantation at different stages of keratoconus. Acta Ophthalmol. 2016 Apr 30.	Wrong study design: single-arm study with less than 50 eyes.
16.	Fernández-Velázquez FJ, Fernández-Fidalgo MJ. Feasibility of custom-made hydrogel contact lenses in keratoconus with previous implantation of intracorneal ring segments. Cont Lens Anterior Eye. 2015 Oct;38(5):351-6.	Wrong intervention.
17.	Stival LR, Nassaralla BR, Figueiredo MN, Bicalho F, Nassaralla Junior JJ. Intrastromal corneal ring segment implantation for ectasia after refractive surgery. Arq Bras Oftalmol. 2015 Jul-Aug;78(4):212-5.	Wrong study design: single-arm study with less than 50 eyes.
18.	Hashemi H, Amanzadeh K, Miraftab M, Asgari S. Femtosecond-assisted intrastromal corneal single-segment ring implantation in patients with keratoconus: a 12-month follow-up. Eye Contact Lens. 2015 May;41(3):183-6.	Wrong intervention.
19.	Ibrahim O, Elmassry A, Said A, Abdalla M, El Hennawi H, Osman I. Combined femtosecond laser-assisted intracorneal ring segment implantation and corneal collagen cross-linking for correction of keratoconus. Clin Ophthalmol. 2016 Mar 22;10:521-6.	Wrong intervention.
20.	Ong JA, Auvinet E, Forget KJ, Lagali N, Fagerholm P, Griffith M, Meunier J, Brunette I. 3D Corneal Shape After Implantation of a Biosynthetic Corneal Stromal Substitute. Invest Ophthalmol Vis Sci. 2016 May 1;57(6):2355-65.	Wrong intervention.
21.	Mojaled Nobari S, Villena C, Jadidi K. Full-Ring Intracorneal Implantation in Corneas With Pellucid Marginal Degeneration. Iran Red Crescent Med J. 2015 Dec 26;17(12):e28974.	Wrong intervention.
22.	Ganesh S, Brar S. Femtosecond Intrastromal Lenticular Implantation Combined With Accelerated Collagen Cross-Linking for the Treatment of Keratoconus--Initial Clinical Result in 6 Eyes. Cornea. 2015 Oct;34(10):1331-9.	Wrong intervention.
23.	Kramer EG, Boshnick EL. Scleral lenses in the treatment of post-LASIK ectasia and superficial neovascularization of intrastromal corneal ring segments. Cont Lens Anterior Eye. 2015 Aug;38(4):298-303.	Wrong study design: single-arm study with less than 50 eyes.
24.	Fahd DC, Alameddine RM, Nasser M, Awwad ST. Refractive and topographic effects of single-segment intrastromal corneal ring segments in eyes with moderate to severe keratoconus and inferior cones. J Cataract Refract Surg. 2015 Jul;41(7):1434-40.	Wrong study design: retrospective.
25.	Ferenczy PA, Dalcegio M, Koehler M, Pereira TS, Moreira H, Luciane Bugmann M. Femtosecond-assisted intrastromal corneal ring implantation for keratoconus treatment: a comparison with crosslinking combination. Arq Bras Oftalmol. 2015 Mar-Apr;78(2):76-81.	Wrong study design: retrospective.
26.	Beniz LA, Queiroz GH, Queiroz CF, Lopes WL, Moraes LF, Beniz J. Intrastromal corneal ring segments delay corneal grafting in patients with keratoconus. Arq Bras Oftalmol. 2016 Feb;79(1):30-2.	Wrong study design: single-arm study with less than 50 eyes.
27.	Vega-Estrada A, Alio JL. The use of intracorneal ring segments in keratoconus. Eye Vis (Lond). 2016 Mar 15;3:8.	Background.
28.	Jadidi K, Mosavi SA, Nejat F, Naderi M, Janani L, Serahati S. Intrastromal corneal ring segment implantation (keraring 355°) in patients with central keratoconus: 6-month follow-up. J Ophthalmol. 2015;2015:916385.	Wrong study design: single-arm study with

		less than 50 eyes.
29.	Kumar M, Shetty R, Kumar RS, Nagaraj S, Shetty B. Use of Wavefront Imaging Technology to Demonstrate Improvement in Corneal Aberrations Using Piggyback Contact Lens in a Keratoconus Eye With Intrastromal Corneal Ring Segment Implantation: A Case Report. Eye Contact Lens. 2016 May;42(3):e12-6.	Wrong study design: single-arm study with less than 50 eyes.
30.	Rai RR, Messenger WB, Ambati BK. Hydrogel ocular sealant for wound closure during intrastromal corneal ring segment implantation. J Cataract Refract Surg. 2016 Apr;42(4):515-9.	Wrong study design: retrospective.
31.	Saib N, Bonnel S, Fenolland JR, Abrieu M, Rambaud C, Berguiga M, Froussart-Maille F, Rigal-Sastourne JC. Intrastromal corneal rings and corneal collagen crosslinking for progressive keratoconus: comparison of two sequences. Eye (Lond). 2015 Feb;29(2):294-5.	Wrong study design: no study.
32.	Liu XL, Li PH, Fournie P, Malecaze F. Investigation of the efficiency of intrastromal ring segments with cross-linking using different sequence and timing for keratoconus. Int J Ophthalmol. 2015 Aug 18;8(4):703-8.	Wrong study design: single-arm study with less than 50 eyes.
33.	Israel M, Yousif MO, Osman NA, Nashed M, Abdelfattah NS. Keratoconus correction using a new model of intrastromal corneal ring segments. J Cataract Refract Surg. 2016 Mar;42(3):444-54.	Wrong study design: single-arm study with less than 50 eyes.
34.	Sachdev G, Sachdev MS, Sachdev R, Gupta H. Unilateral corneal ectasia following small-incision lenticule extraction. J Cataract Refract Surg. 2015 Sep;41(9):2014-8.	Wrong study design: single-arm study with less than 50 eyes.
35.	Kamiya K, Shimizu K, Igarashi A, Miyake T. Assessment of Anterior, Posterior, and Total Central Corneal Astigmatism in Eyes With Keratoconus. Am J Ophthalmol. 2015 Nov;160(5):851-857.e1.	Wrong research question.
36.	Janunts E, Langenbucher A, Seitz B.In Vitro Corneal Tomography of Donor Cornea Using Anterior Segment OCT. Cornea. 2016 May;35(5):647-53.	Wrong population.
37.	Ibares-Frías L, Gallego P, Cantalapiedra-Rodriguez R, Merayo-Lloves J, Martínez-García MC. Clinical, Refractive and Histological Reversibility of Corneal Additive Surgery in Deep Stroma in an Animal Model. Curr Eye Res. 2016 Feb 18:1-10.	Wrong population.
38.	Parker JS, van Dijk K, Melles GR. Treatment options for advanced keratoconus: A review. Surv Ophthalmol. 2015 Sep-Oct;60(5):459-80.	Background.
39.	Janani L, Jadidi K, Mosavi SA, Nejat F, Naderi M, Nourijelyani K. MyoRing Implantation in Keratoconic Patients: 3 years Follow-up Data. J Ophthalmic Vis Res. 2016 Jan-Mar;11(1):26-31.	Wrong study design: single-arm study with less than 50 eyes.
40.	McGhee CN, Kim BZ, Wilson PJ. Contemporary Treatment Paradigms in Keratoconus. Cornea. 2015 Oct;34 Suppl 10:S16-23.	Background.
41.	Assaf A, Kotb A. Simultaneous corneal crosslinking and surface ablation combined with phakic intraocular lens implantation for managing keratoconus. Int Ophthalmol. 2015 Jun;35(3):411-9.	Wrong intervention.
42.	Zare MA, Mehrjardi HZ, Afarideh M, Bahrmandy H, Mohammadi SF. Visual, Keratometric and Corneal Biomechanical Changes after Intacs SK Implantation for Moderate to Severe Keratoconus. J Ophthalmic Vis Res. 2016 Jan-Mar;11(1):17-25.	Wrong study design: single-arm study with less than 50 eyes.
43.	Carracedo G, Blanco MS, Martin-Gil A, Zicheng W, Alvarez JC, Pintor J. Short-term Effect of Scleral Lens on the Dry Eye Biomarkers in Keratoconus. Optom Vis Sci. 2016 Feb;93(2):150-7.	Wrong population.
44.	Mohamed-Noriega K, Butrón-Valdez K, Vazquez-Galvan J, Mohamed-Noriega J, Cavazos-Adame H, Mohamed-Hamsho J. Corneal Melting after Collagen Cross-Linking for Keratoconus in a Thin Cornea of a Diabetic Patient Treated with Topical Nepafenac: A Case Report with a Literature Review. Case Rep Ophthalmol. 2016 Feb 26;7(1):119-24.	Wrong study design: single-arm study with less than 50 eyes.

45.	Spadea L, Salvatore S, Verboschi F, Vingolo EM. Corneal collagen cross-linking followed by phacoemulsification with IOL implantation for progressive keratoconus associated with high myopia and cataract. Int Ophthalmol. 2015 Oct;35(5):727-31.	Wrong study design: single-arm study with less than 50 eyes.
46.	Matsumoto Y, Dogru M, Shimazaki J, Tsubota K. Novel corneal piggyback technique for consecutive intraocular lens implantation and penetrating keratoplasty surgery. Cornea. 2015 Jun;34(6):713-6.	Wrong study design: single-arm study with less than 50 eyes.
47.	Mohebbi M, Hashemi H, Asgari S, Bigdeli S, Zamani KA. Visual outcomes after femtosecond assisted intracorneal MyoRing implantation: 18 months of follow-up. Graefes Arch Clin Exp Ophthalmol. 2016 May;254(5):917-22.	Wrong study design: single-arm study with less than 50 eyes.
48.	Kamiya K, Shimizu K, Miyake T. Changes in astigmatism and corneal higher-order aberrations after phacoemulsification with toric intraocular lens implantation for mild keratoconus with cataract. Jpn J Ophthalmol. 2016 May 10.	Wrong study design: single-arm study with less than 50 eyes.
49.	Chhadva P, Yesilirmak N, Cabot F, Yoo SH. Intrastromal Corneal Ring Segment Explantation in Patients With Keratoconus: Causes, Technique, and Outcomes. J Refract Surg. 2015 Jun;31(6):392-7.	Wrong study design: single-arm study with less than 50 eyes.
50.	Sideroudi H, Labiris G, Soto-Beobide A, Voyiatzis G, Chrissanthopoulos A, Kozobolis V.The effect of collagen cross-linking procedure on the material of intracorneal ring segments. Curr Eye Res. 2015 May;40(6):592-7.	Wrong research question.
51.	Kamiya K, Shimizu K, Kobashi H, Igarashi A, Komatsu M, Nakamura A, Kojima T, Nakamura T. Three-year follow-up of posterior chamber toric phakic intraocular lens implantation for the correction of high myopic astigmatism in eyes with keratoconus. Br J Ophthalmol. 2015 Feb;99(2):177-83.	Wrong study design: retrospective.
52.	Graue-Hernandez EO, Pagano GL, Garcia-De la Rosa G, Ramirez-Miranda A, Cabral-Macias J, Lichtinger A, Abdala-Figuerola A, Navas A. Combined small-incision lenticule extraction and intrastromal corneal collagen crosslinking to treat mild keratoconus: Long-term follow-up. J Cataract Refract Surg. 2015 Nov;41(11):2524-32.	Wrong study design: single-arm study with less than 50 eyes.
53.	Antonios R, Dirani A, Fadlallah A, Chelala E, Hamade A, Cherfane C, Jarade E. Safety and Visual Outcome of Visian Toric ICL Implantation after Corneal Collagen Cross-Linking in Keratoconus: Up to 2 Years of Follow-Up. J Ophthalmol. 2015;2015:514834.	Wrong study design: single-arm study with less than 50 eyes.
54.	Sadigh AL, Aali TA, Sadeghi A. Outcome of intrastromal corneal ring segment relative to depth of insertion evaluated with scheimpflug image. J Curr Ophthalmol. 2015 Oct 29;27(1-2):25-31.	Wrong study design: retrospective.
55.	Barbara R, Barbara A, Naftali M. Depth evaluation of intended vs actual intacs intrastromal ring segments using optical coherence tomography. Eye (Lond). 2016 Jan;30(1):102-10.	Wrong study design: single-arm study with less than 50 eyes.
56.	Preussner PR, Hoffmann P, Wahl J. Impact of Posterior Corneal Surface on Toric Intraocular Lens (IOL) Calculation. Curr Eye Res. 2015;40(8):809-14.	Wrong intervention.
57.	Hashemi H, Heidarian S, Seyedian MA, Yekta A, Khabazkhoob M. Evaluation of the Results of Using Toric IOL in the Cataract Surgery of Keratoconus Patients. Eye Contact Lens. 2015 Nov;41(6):354-8.	Wrong study design: single-arm study with less than 50 eyes.
58.	Carracedo G, Wang Z, Serramito-Blanco M, Martin-Gil A, Carballo-Alvarez J, Pintor J. Ocular Surface Temperature During Scleral Lens Wearing in Patients With Keratoconus. Eye Contact	Wrong study design: single-

	Lens. 2016 May 19.	arm study with less than 50 eyes.
59.	Veldman PB, Dye PK, Holiman JD, Mayko ZM, Sáles CS, Straiko MD, Galloway JD, Terry MA. The S-stamp in Descemet Membrane Endothelial Keratoplasty Safely Eliminates Upside-down Graft Implantation. Ophthalmology. 2016 Jan;123(1):161-4.	Wrong intervention.
60.	Al Muammar A. Comparison of visual, refractive and topographic keratometry outcomes of Intacs and Intacs SK in mild to moderate keratoconus eyes. Middle East Afr J Ophthalmol. 2015 Jan-Mar;22(1):74-9.	Wrong study design: retrospective.
61.	Gokul A, Krishnan T, Emanuel PO, Saunders M, McGhee CNj. Persisting extreme acute corneal hydrops with a giant intrastromal cleft secondary to keratoconus. Clin Exp Optom. 2015 Sep;98(5):483-6.	Wrong population.
62.	Hosny M, El-Mayah E, Sidky MK, Anis M. Femtosecond laser-assisted implantation of complete vs. incomplete rings for keratoconus treatment. Clin Ophthalmol. 2015 Jan 20;9:121-7.	Wrong study design: single-arm study with less than 50 eyes.
63.	Zhang T, Sun Y, Liu M, Zhou Y, Wang D, Chen Y, Liu Q. Femtosecond Laser-assisted Endokeratophakia Using Allogeneic Corneal Lenticule in a Rabbit Model. J Refract Surg. 2015 Nov;31(11):775-82.	Wrong population.
64.	Yahia Chérif H, Gueudry J, Afriat M, Delcampe A, Attal P, Gross H, Muraine M. Efficacy and safety of pre-Descemet's membrane sutures for the management of acute corneal hydrops in keratoconus. Br J Ophthalmol. 2015 Jun;99(6):773-7.	Wrong intervention.
65.	Daxer A, Ettl A, Hörantner R. Long-term results of MyoRing treatment of keratoconus. J Optom. 2016 Feb 25. pii: S1888-4296(16)00004-2.	Wrong study design: retrospective.
66.	Ghanem RC, Bogoni A, Ghanem VC.Pachymetry-guided intrastromal air injection ("pachy-bubble") for deep anterior lamellar keratoplasty: results of the first 110 cases. Cornea. 2015 Jun;34(6):625-31.	Wrong intervention.
67.	Rajabi MT, Makateb A, Hashemi H, Holland EJ, Djalilian A, Nerad JA. Disaster in Cosmetic Surgery: Inadvertent Formalin Injection During Blepharoplasty. Ophthal Plast Reconstr Surg. 2015 Jul-Aug;31(4):e86-9.	Wrong study design: single-arm study with less than 50 eyes.
68.	Stelton CR, Townsend J, Peterson LT, Khurana RN, Yeh S. Surgical Management of Anterior Chamber Migration of a Dexamethasone Intravitreal Implant. Ophthalmic Surg Lasers Imaging Retina. 2015 Jul-Aug;46(7):756-9.	Wrong study design: single-arm study with less than 50 eyes.
69.	Shetty R, Kaweri L, Pahuja N, Nagaraja H, Wadia K, Jayadev C, Nuijts R, Arora V. Current review and a simplified "five-point management algorithm" for keratoconus. Indian J Ophthalmol. 2015 Jan;63(1):46-53.	Background.
70.	Pásztor D, Kolozsvári BL, Losonczy G, Fodor M. Femtosecond laser-assisted keratoplasty combined with cataract extraction in a patient with keratoconus and oculocutaneous albinism. Indian J Ophthalmol. 2016 Mar;64(3):246-8.	Wrong study design: single-arm study with less than 50 eyes.
71.	Franch A, Birattari F, Dal Mas G, Lužnik Z, Parekh M, Ferrari S, Ponzin D. Evaluation of Intrastromal Riboflavin Concentration in Human Corneas after Three Corneal Cross-Linking Imbibition Procedures: A Pilot Study. J Ophthalmol. 2015;2015:794256.	Wrong intervention.
72.	Soria J, Villarrubia A, Merayo-Lloves J, Elortza F, Azkargorta M, Alvarez de Toledo J, Rodriguez-Agirretxe I, Suarez T, Acera A. Label-free LC-MS/MS quantitative analysis of aqueous humor from keratoconic and normal eyes. Mol Vis. 2015 Apr 25;21:451-60.	Wrong study design: single-arm study with less than 50 eyes.
73.	Knezović I, Belovari Višnjić M, Raguž H. Late Stage of Corneal Decompensation Caused by Progressive Keratoconus: Can We Treat It and Save the Cornea? Case Rep Ophthalmol Med. 2015;2015:795826.	Wrong study design: single-arm study with less than 50

		eyes.
74.	Blum M, Täubig K, Gruhn C, Sekundo W, Kunert KS. Five-year results of Small Incision Lenticule Extraction (ReLEx SMILE). Br J Ophthalmol. 2016 Jan 8. pii: bjophthalmol-2015-306822.	Wrong intervention.
75.	Hamzaoglu EC, Straiko MD, Mayko ZM, Sáles CS, Terry MA. The First 100 Eyes of Standardized Descemet Stripping Automated Endothelial Keratoplasty versus Standardized Descemet Membrane Endothelial Keratoplasty. Ophthalmology. 2015 Nov;122(11):2193-9.	Wrong intervention.
76.	Au J, Goshe J, Dupps WJ Jr, Srivastava SK, Ehlers JP. Intraoperative Optical Coherence Tomography for Enhanced Depth Visualization in Deep Anterior Lamellar Keratoplasty From the PIONEER Study. Cornea. 2015 Sep;34(9):1039-43.	Wrong intervention.
77.	Al-Arfai KM, Yassin SA, Al-Beshri AS, Al-Jindan MY, Al-Tamimi ER. Indications and techniques employed for keratoplasty in the Eastern province of Saudi Arabia: 6 years of experience. Ann Saudi Med. 2015 Sep-Oct;35(5):387-93.	Wrong intervention.
78.	Costa JF, Rego M, Rosa A, Costa E, Fonseca P, Cachulo ML, Veríssimo J, Quadrado MJ, Murta J. Anterior Chamber Epithelial Cyst After Uneventful Deep Anterior Lamellar Keratoplasty. Cornea. 2016 May 4.	Wrong study design: single-arm study with less than 50 eyes.
79.	Lim SH. Clinical applications of anterior segment optical coherence tomography. J Ophthalmol. 2015;2015:605729.	Wrong intervention.
80.	Muñoz G, Rohrweck S, Sakla HF, Altroudi W. Pinhole iris-fixated intraocular lens for dysphotopsia and photophobia. J Cataract Refract Surg. 2015 Mar;41(3):487-91.	Wrong study design: single-arm study with less than 50 eyes.
81.	Schornack MM. Scleral lenses: A literature review. Eye Contact Lens. 2015;41:3–11	Wrong intervention.
82.	Ozgurhan EB, Celik U, Bozkurt E, Demirok A. Evaluation of subbasal nerve morphology and corneal sensation after accelerated corneal collagen crosslinking treatment on keratoconus. Current Eye Research. 2015;40:484–489.	Wrong research question.
83.	Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio R Jr, Guell JL, Malecaze F, Nishida K, Sangwan VS. Global consensus on keratoconus and ectatic diseases. Cornea. 2015;34:359–369	Background.

Cochrane risk of bias checklist for randomized controlled trial

Table VIII. Risk of bias for randomized controlled trial.

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk.	Quote: "consecutive randomized study <…> patients were included and were randomly divided into two groups" Comment: Probably done.
Allocation concealment (selection bias)	Low risk.	Quote: "the eyes were randomly divided into two groups" Comment: Probably done.
Blinding of participants and personnel (performance bias)	High risk.	Comment: Probably not done.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	High risk.	Comment: Probably not done.
Blinding of outcome assessment (detection bias) (Mortality)	High risk.	Comment: Probably not done.
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	High risk.	Comment: Probably not done.
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	High risk.	Comment: Probably not done.
Selective reporting (reporting bias)	High risk.	Only primary outcomes reported.

Quality assessment of the systematic reviews

Table IX. Quality assessment of the selected systematic reviews.

	Fischer, 2015 [19]	Ziaei, 2015 [24]	Mandathara, 2015 [29]
1.Was an 'a priori' design provided?	Yes	No	Yes
2.Was there duplicate study selection and data extraction?	Yes	CA	CA
3.Was a comprehensive literature search performed?	Yes	No	No
4.Was a status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No	No
5.Was a list of studies (included and excluded) provided?	No	No	No
6.Were the characteristics of the included studies provided?	Yes	Yes	CA
7.Was the scientific quality of the included studies assessed and documented?	Yes	No	CA
8.Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	No	CA
9.Were the methods used to combine the findings of studies appropriate?	No	No	No
10.Was the likelihood of publication bias assessed?	No	No	No
11.Was the conflict of interest included?	No	No	No

*CA – Can't answer.

The AMSTAR checklist for systematic reviews

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.
Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."
□ Yes
□ No
□ Can't answer
□ Not applicable

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.
□ Yes
□ No
□ Can't answer
□ Not applicable

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.
Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).
□ Yes
□ No
□ Can't answer
□ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.
Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.
□ Yes
□ No
□ Can't answer
□ Not applicable

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.
Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."
□ Yes
□ No
□ Can't answer
□ Not applicable

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.
Note: Acceptable if not in table format as long as they are described as above.
□ Yes
□ No
□ Can't answer
□ Not applicable

7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.
Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).
□ Yes
□ No
□ Can't answer
□ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.
Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.
□ Yes
□ No
□ Can't answer
□ Not applicable

9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).
Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.
□ Yes
□ No
□ Can't answer
□ Not applicable

10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).
Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
□ Yes
□ No
□ Can't answer
□ Not applicable

11. Was the conflict of interest included?
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.
Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.
□ Yes
□ No
□ Can't answer
□ Not applicable

Shea et al. BMC Medical Research Methodology 2007 **7**:10 doi:10.1186/1471-2288-7-10.
Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

Checklist for potential ethical, organisational, social and legal aspects

Table X. Checklist for potential ethical, organisational, social and legal aspects.

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparators require organisational changes?	No
2.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be organisationally relevant?	No
3. Social	
3.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be socially relevant?	No
4. Legal	
4.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be legally relevant?	No