# Effectiveness of Matching Human Leukocyte Antigens (HLA) in Corneal Transplantation: A Systematic Review Protocol

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**Protocol**

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# Effectiveness of matching Human Leukocyte Antigens (HLA) in corneal transplantation: a systematic review protocol

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## Abstract

### Background

Corneal transplantation is the most frequently performed transplantation. Despite this, the therapeutic value of matching Human Leukocyte Antigen (HLA) subtypes for transplanted corneas remains controversial. Ocular immune privilege was originally deemed to render matching unnecessary; however more recently, matching has demonstrated improved outcomes including graft success, amongst others. This systematic review aims to evaluate the effectiveness of major and minor antigen matching on graft outcomes in corneal transplantation.

### Methods

Standard systematic review methodology will be used to identify, select and extract data from observational studies and clinical trials assessing the effects of HLA matching on corneal graft outcomes. Bibliographic databases (Cochrane Library, EMBASE, MEDLINE, Web of Science, Scopus), clinical trial registers, abstract and conference proceedings, in addition to dissertation, thesis and grey literature will be searched. Neither date of publication nor language will be restricted, and non-English articles will be translated were necessary. The primary outcome will be to assess corneal graft success for different degrees of HLA matching/mismatching. The precise end outcome measure varies amongst studies and includes graft rejection, immunoreaction, failure and survival. Therefore, data will be extracted across all relevant outcome parameters and grouped for subsequent statistical tests. Risk of bias assessment will be completed, appropriate to each study design. Study selection, data extraction and risk of bias assessment will be independently completed by two reviewers. Data will be tabulated, and a narrative synthesis presented. Meta-analysis will be performed where there is sufficient homogeneity between studies to warrant its effective completion. Subgroup and sensitivity analysis will be undertaken if appropriate.

### Discussion

Many studies have investigated the effectiveness of HLA matching for corneal transplantation. A systematic review is needed to collate and analyse this evidence. Findings of this systematic review may form the basis of evidence-based recommendations on pre-operative HLA typing and matching of corneal grafts for transplantation.

### Systematic Review Registration

PROSPERO reference CRD42020198882

**Keywords**

Systematic review; meta-analysis; corneal transplantation, keratoplasty; antigen matching; HLA matching; rejection; reaction; failure; survival.

## Background

Amongst preventable and untreated causes, corneal blindness is the fourth most common cause of visual impairment worldwide.[1,2] Corneal transplantation is the only effective sight restoring intervention for corneal blindness. It is the most frequently performed transplantation in the UK with over 4000 procedures annually since 2016.[3,4] It is an intervention of unmet demand, with disproportionately low supplies of donor corneas available in countries with the highest rates of corneal transplantation.[5] This disparity has detrimental consequences for a treatable population of patients with corneal blindness.

The most common indications for corneal transplantation in the UK remain Keratoconus, pseudophakic bullous keratopathy, Fuch's endothelial dystrophy, infection and graft failure.[4] There are various techniques for corneal transplantation and the field has observed significant advances over recent decades. While the indication determines the precise type of transplantation procedure, full thickness and anterior lamellar grafts constitute over a third of the corneal transplants performed in the UK.[4]

Corneal transplantation is regarded as one of the most successful transplantation procedures attributed principally to the cornea being an immunologically privileged site.[6] Despite the relatively lower immunogenicity of the cornea and the use of post-operative prophylactic treatment, 20 to 30% of corneal transplant patients still experience at least one episode of acute rejection within the first 5 years.[7,8,9] Successful reversal of the rejection episode is reported in 50% to 90% of cases.[10] However, in cases where the acute rejection is persistent, graft failure may ensue.[11]

Rejection and graft failure are more commonly observed amongst high-risk corneal transplants. A number of high-risk factors are reported in the literature with the most well recognised being underlying ocular surface inflammatory conditions, re-transplantation, corneal neovascularization and neolymphangiogenesis, glaucoma, previous ocular surgery, and male to female transplantation.[12] In these high-risk cases, rejection can occur in 30 to 60% of grafts, with up to a 70% graft failure rate within 10 years - despite local or systemic immunosuppressive therapy.[13,14,15]

Human Leukocyte Antigen (HLA) matching is recommended for other organ transplantations to offer the best opportunity for graft success.[16,17,18] However, the evidence supporting HLA typing for corneal transplantation remains less clear, with no international consensus.

Scoping of the literature revealed a summary document for a 1995 systematic review, which pooled results from 8 studies from 1966 to 1995, concluding that there was a non-significant effect of HLA-DR mismatching on first graft rejection: RR -0.13 (95% CI: -0.35, 0.09).[19] However, specific questions about the methodology, including study selection and analysis were indeterminable from this report.

More recently, a 2015 narrative review discussed the value of major and minor HLA matching on corneal transplantation outcomes. They included thirty studies from 1974 to 2006 and concluded that despite controversial results being presented in older studies, recent evidence suggests HLA matching is beneficial for corneal allograft survival in general and even more significantly in high-risk allografts.[20] However, this conclusion was based on common themes amongst the outcome data and standard systematic review methodology was not used.

HLA matching does not form part of the current corneal allocation policy in the UK.[1] Considering recent work within this active field, the proposed systematic review aims to evaluate the existing literature to determine the effect of HLA matching on corneal transplantation success. This may form the basis of evidence-based recommendations for future clinical practice.

## Methods

### Aims

To assess the effectiveness of HLA matching for corneal transplantation. This will be achieved through the completion of a systematic review of the studies:

- Assessing the effect of major antigen matching on graft outcomes
- Assessing the effect of minor antigen matching on graft outcomes

The protocol for this systematic review was registered with the PROSPERO database (reference CRD42020198882).[21] The review and its findings are reported in accordance with PRISMA guidelines.[22] A PRISMA-P checklist for this protocol is shown in **Additional File 1**.

### Searches

The following sources will be searched between summer and autumn 2020, with no date restriction applied:

- The Cochrane Library (CENTRAL Register of Controlled Trials)
- EMBASE
- MEDLINE, MEDLINE in process (Ovid)
- Web of Science
- Scopus

Registers of clinical trials

- WHO International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/ictrp/)
- European Clinical Trials Database (EudraCT)
- Clinicaltrials.gov (www.clinicaltrials.gov)
- International Standard Randomised Controlled Trials Number Database (ISRCTN)
- UK Clinical Research Network (www.ukcrn.org.uk)

Abstract and conference proceedings:

- Conference Proceedings Citation Index (Web of Science)
- British library ZETOC

Dissertations, theses and grey literature:

- ProQuest (www.proquest.com)
- OpenGrey (www.opengrey.eu)
- British Library Ethos

For bibliographic databases, the search strategy will combine index and free terms for the surgical procedure and distinctive lamellar techniques.

A sample strategy from MEDLINE has been formulated to collate all relevant evidence, and this has been included as **Appendix 1**. For each of the databases above, the search strategy may be adapted as deemed appropriate. An iterative manner will be applied to complete the search from these sources. The bibliographic references of the 1995 systematic review and any appropriate evidence reviews will be hand searched to ensure that no relevant primary study has been missed. Furthermore, a clinical expert will be contacted to ensure no similar systematic reviews are currently ongoing. To collate a comprehensive range of evidence, no restrictions will be placed by either publication date or language. RefWorks and Rayyan will be used to manage the search results. This will also enable exclusion of any duplicate entries, study details and references. Grey literature will also be searched alongside electronic databases to reduce the risk of publication bias being introduced into the systematic review.

**Selection criteria**

The following criteria will be utilised to select studies for this review:

- PICO Framework

| | |
|---|---|
| Population | Patients (humans) undergoing corneal transplantation |
| Intervention | Donor-recipient HLA matching |
| Comparator | Patients receiving unmatched/ selectively matched/ or randomly allocated donor corneas |
| Outcome | Occurrence of rejection and failure |

**Table 1:** PICO framework used to generate this review

- Study design:
    - RCTs, non-RCT trial-based studies and cohort studies.

- Participants:
    - Patients of any age, gender or ethnicity undergoing any form of corneal transplant. No restriction on date of transplantation will be applied.
- Intervention and comparator
    - Comparing the use of major antigen matching to antigen mismatching.
    - Comparing the use of minor antigen matching to antigen mismatching.
- Outcomes
    - Primary outcome
        - Corneal graft prognosis in the post-operative period: number of graft rejections, immunoreactions, failure and/or survival

With the exception of limbal, endothelial and tectonic transplants, all type of corneal transplant will be analysed.

Major antigen studies will be defined as those that discuss the effect of MHC class I (HLA-A, HLA-B and HLA-C), class II (HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA and HLA-DRB1) and/or class III genes.[23] As there are an abundance of minor antigen sub-types [24], any studies including histocompatibility complexes not concerning the aforementioned antigens will be considered as minor.

All types of corneal transplant will be eligible for inclusion regardless of the underlying disease it was used to treat. However, it is important to note that grafts for keratoconus and other non-inflammatory conditions are likely to have better outcomes, compared to outcomes in patients with inflammatory diseases and re-grafts. The analysis of the studies may therefore be grouped based on the underlying disease, should the studies permit such stratification. Studies that include both the assessment of major and minor antigen matching will also be included in this review.

**Selection process**

Selection of studies will be in two stages:

1. Abstracts and titles of each study will be screened to exclude unnecessary data.
2. Potentially relevant studies will have their full texts extracted and assessed against the selection criteria.

The appropriateness of articles will be assessed independently by two reviewers (JPC and SSK). A third reviewer (GB) will resolve any conflicts of opinion between each assessment. This process will be outlined through a PRISMA flow diagram. Exclusion of studies will be recorded and discussed in this review, and any non-English language studies will be translated to allow for a fuller inclusion of relevant studies.

**Data extraction**

Relevant data from the suitable studies will be extracted independently by two individual authors. Any differences in opinion will be settled by discussion between both authors. If insufficient, this will be followed by a referral to a third author to resolve the matter at hand. A standardised data collection form in Microsoft Excel will be created and used by the authors to summarise the extracted data. The study authors and publishing bodies may be contacted if any relevant information is missing from the reviewed studies. For each study the following information, but not limited to, will be extracted:

- Study characteristics
    - Authors, publication year, title and journal
    - Study design
    - Setting/location
    - Sample size
    - Length of follow-up and variability in post-operative treatment
    - Analysis
- Participant characteristics
    - Patient selection and recruitment criteria
    - Demographic data-number, age, gender, socioeconomic status and ethnicity
    - Past ocular history
- Intervention and comparator
    - Donor-recipient HLA matching
    - Comparator: patients receiving unmatched/randomly allocated donor corneas
    - Any differences in underlying care between the treatment groups
- Outcomes and findings
    - Number of graft rejections/reactions/failures at pre-defined follow-up intervals
    - Graft survival times (time to rejection and time to failure)

- Adverse events (including side effects and complications of treatment)
- Precision and statistical test results for each outcome
- Completeness of follow-up for each outcome

**Quality assessment**

The quality of all the included studies will be assessed independently by two reviewers. Any disagreements will be resolved by discussion between the two individuals. If necessary, a third reviewer will act as an impartial mediator. RCTs will be assessed using the Cochrane Handbook Risk of Bias tool (RoB 2).[25] This will also be used to assess non-randomised trials, hence it is understood that the criteria present in this tool for allocation concealment and randomisation will not be relevant. Any prospective controlled observational studies will be assessed using the guidelines present in Chapter 13 of the Cochrane Handbook.[25] The RoB 2 tool may also be used as a minimum assessment - again without all criteria of the tool being relevant for this type of study. In prospective observational studies, the most relevant information to evaluate is the group selection criteria, differences in patient characteristics, losses to follow-up, biases and other confounders. The assessment of the biases present in each of the included studies will be collated in a findings table. In particular, the authors acknowledge that there may be variation in the definition of the study endpoints across the literature and this will, therefore, be interrogated as a source of bias.

**Analysis**

Included studies will be grouped based on the type of corneal transplant used (intervention) and the outcome parameters measured. It may be necessary to further stratify the studies based on the underlying disease state. The data will be tabulated and a narrative synthesis of the relevant evidence compiled for each outcome of relevance to the review. This will aid with the summary of findings from each study and help to identify patterns in the data. Bias within studies will be quantitatively assessed and tabulated using risk of bias tools.

A decision on whether a fixed-effects or random-effects meta-analysis is to be performed will be made based on study heterogeneity and whether there is sufficient homogeneity to warrant its effective completion.[26] Heterogeneity will be determined in the context of percentage variation in study results (using the $I^2$ statistic) and variance of effect size (using the tau-squared statistic).

Data pooling will be carried out for the purpose of generating a Forest Plot, which will serve as a visual representation of the pooled effect of the said data. However, data from studies with variable study designs will not be pooled together.

Where heterogeneity is significant in studies, subgroup analysis may be conducted in order to investigate the source of heterogeneity, if the completeness of a study's data collection and reporting allows for this. Given the high variability in follow-up periods across the studies to be analysed, time-specific data from the post-operative period might have to be grouped where appropriate. Alternatively, outcome data may be grouped across all post-operative periods if better suited.

## Reporting

The results of this systematic review and associated meta-analysis will be reported using guidance laid out by the PRISMA reporting tool.[22] This will be done with the intention of ensuring the reporting of results is both complete and transparent, under a well-recognised checklist.

The robustness of the review methodology will be discussed. An examination of both the internal and external validity of the results will also be conducted, for a complete picture of the integrity of the evidence base on which this review will be founded.

Following this, the implications of this review for future research, practice, health guideline revision and implementation will be considered.

## Discussion and Potential Impact

Immunological compatibility, as with other tissue grafts, may have a beneficial effect for improving corneal graft prognosis following transplantation. However, the current lack of consensus between existing evidence has led to the absence of HLA matching for corneal grafts. This review will comprehensively and systematically extract published evidence from a multitude of sources. This protocol will be the first of its kind to be published, and the first to be registered prospectively.

The aim of this systematic review will be to reach an overall verdict regarding the effects of antigen matching of corneal grafts on survival; ultimately to aid with the improvement of patient outcomes.

**Abbreviations**

HLA: Human Leukocyte Antigen

MHC: Major Histocompatibility Complex

PICO: Problem/Patient/Population, Intervention/Indicator, Comparison, Outcome

EMBASE: Excerpta Medica Database

CENTRAL: Cochrane Central Register of Controlled Trials

MEDLINE: Medical Literature analysis and Retrieval System Online

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT: Randomized Controlled Trial

## Declarations

Ethics approval and consent to participate: not applicable.

Consent for publication: not applicable.

Availability of data and material: not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

GSS, JPC, SSK and DLK contributed to the development of this protocol and drafted the protocol manuscript. KAT and AK are proposed to support the risk of bias assessment and synthesis of the final manuscript. RJB and GFB provided clinical advice and reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgements: not applicable.

Documenting amendments:

Any protocol amendments will be clearly recorded to distinguish from the original submission. These may be further explored during the evaluation stage of the final systematic review, should these amendments be deemed significant.

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**Appendix 1:** Ovid Embase sample search strategy

| | | |
|---|---|---|
| ☐ | 1 | exp cornea transplantation/ or (cornea* adj5 (transplant* or graf* or allograf*)).mp. or (exp penetrating keratoplasty/ or exp deep lamellar endothelial keratoplasty/ or exp endothelial keratoplasty/ or exp refractive keratoplasty/ or exp descemet stripping endothelial keratoplasty/ or exp keratoplasty/) or keratoplast*.mp. or ((penetrat* or penatrat* or strip* or endotheli* or refract* or reflect*) adj5 keratoplast*).mp. or ((desceme* or membran* or deep or lamellar or ant* or post* or automat*) adj5 keratoplast*).mp. or ((cornea* or keratoplast* or transplant*) and (DMEK or DSAEK or DSEK or DALK or Deep-ALK or ALK or DALKP or LK or LKP or PK or PKP)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] |
| ☐ | 2 | Leukocyte antigen/ or ((leukocyte* or leucocyte*) adj1 (antigen* or antegen*)).mp. or ((tissue* or graf* or allograf* or antigen* or antegen*) adj5 (compat* or match*)).mp. or (Histocompatibility or histocompatibility antigen or histocompatibility complex or major histocompatibility complex or major histocompatibility antigen or minor histocompatibility complex or minor histocompatibility antigen or major histocompatibility antigen class 1 or major histocompatibility antigen class 2 or HLA antigen class 1 or HLA antigen Class 2).mp. or (Histocompat* adj1 (antigen* or antegen* or complex*)).mp. or ((Major or Minor) adj1 (antigen* or antegen*)).mp. or (MHC or MHA or MiHA or HLA or hy or ha3).mp. or (major histocompatibility antigen class 1 or major histocompatibility antigen class 2).mp. or (major histocompat* complex* class adj1 (I or ONE or II or TWO)).mp. or (major histocompat* antigen* class adj1 (I or ONE or II or TWO)).mp. or (major histocompat* complex* class 1 or major histocompat* complex* class1 or major histocompat* complex* class 2 or major histocompat* complex* class2).mp. or (antigen* class 1 or antigen* class1 or antigen* class 2 or antigen* class2).mp. or (HLA antigen* class 1 or HLA antigen* class1 or HLA class 1 or HLA class1 or HLA antigen* class 2 or HLA antigen* class2 or HLA class 2 or HLA class2).mp. or (MHC class 1 or MHC class1 or MHC class 2 or MHC class2).mp. or (HLA class 1 or HLA class1 or HLA class 2 or HLA class2).mp. or (HLA 1 or HLA1 or HLA 2 or HLA2).mp. or (MHC 1 or MHC1 or MHC 2 or MHC2).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] |
| ☐ | 3 | 1 and 2 |
| ☐ | 4 | (case control study or case report or case reports or case study or case control studies or clinical study or cohort analysis or cohort studies or correlational study or cross sectional studies or cross sectional study or epidemiologic studies or family study or follow up or followup studies or follow up studies or hospital based case control study or longitudinal studies or longitudinal study or observational study or population based case control study or prospective studies or prospective study or retrospective studies or retrospective study).sh. or ((((case or cross sectional or crosssectional or epidemiologic* or observation*) adj (study or studys or studies)) or (case adj (control* or report*)) or cohort* or cross sectional or followup* or follow up* or followed or longitudinal* or prospective* or retrospective*).tw. or case reports.pt. or case control* study.mp. or case control* studies.mp. or case control*.mp. or case report*.mp. or case study.mp. or case studie*.mp. or clinical study.mp. or cohort analysis.mp. or cohort study.mp. or cohort studies.mp. or ((case or case control* or clinical or cohort or correlation* or crosssectional or cross sectional or epidemiologic* or family or follow* up or followup or hospital base* case control or longitudinal* or observation* or population base* case control or prospective* or retrospective* or nonconcurrent or non concurrent or noncurrent prospective or nonconcurrent prospective) adj1 (study of studie* or report* or analysed or analysis)).mp. or follow* up.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] |
| ☐ | 5 | (nonequivalent control group or posttesting or pretesting or pretest posttest design or pretest posttest control group design or quasi experimental methods or quasi experimental study or time series or time series analysis or clinical trial or clinical study or trial clinical or non randomi?ed or nonrandomi?ed control* study).sh. or ((((nonequivalent or non equivalent) adj3 control*) or posttest* or posttest* or pre test* or pretest* or quasi experiment* or quasiexperiment* or timeseries or time series or clinical trial or trial clinical or clinical study or nonrandomi?ed or non randomi?ed or control* study or control* studies).tw. |
| ☐ | 6 | (equivalent control group or control* study or control* studies or control* trial or control* clinical trial or (random* adj3 trial)).sh. or ((equivalent adj3 control*) or control* study or control* studies or control* trial or control* clinical trial or (random* adj3 trial)).tw. or ((clinic* or random* or quantitat* or control*) adj1 (trial* or study or studies)).mp. or (random* adj1 (control* or assign* or allocat*)).mp. or (control* adj1 clinic*).mp. or placebo*.mp. or cross* over.mp. or ((singl* or doubl* or tripl* or trebl*) adj1 (blind* or mask*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] |
| ☐ | 7 | (((literature review or systematic review* or meta anal*).sh,pt. or "review literature as topic"/ or ((analy* or evidence* or methodol* or quantativ* or systematic*) adj5 (overview* or review* or synthesis)).tw,sh. or ((analy* or assessment* or evidence* or methodol* or quantativ* or qualitative* or systematic*).ti. and review*.ti,pt.) or (systematic* adj5 (search* or review* or overview*)).ti,ab. or ((electronic database* or bibliographic database* or computeri?ed database* or online database* or (bids or cochrane or pubmed or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or cinahl or science citation or (web adj2 science))).tw,sh. or Cochrane*.sh,tw.)) and (review*.ti,ab,sh,pt. or systematic*.ti,ab.)) or (metaanal* or meta anal* or metasynthes* or meta synethes*).ti,ab,pt,tw,sh. or (research adj1 (review* or integrat*)).ti,ab,tw. or reference list*.ab. or bibliograph*.ab. or published studies.ab. or relevant journals.ab. or selection criteria.ab. or data extraction.ab. or (data adj (extraction or synthesis)).ab. or (handsearch* or hand search* or ((hand or manual) adj2 search*)).ti,ab,tw,sh. or (mantel haenszel or peto or dersimonian or der simonian).ti,ab,tw,sh. or (fixed effect* or random effect*).ti,ab. or Meta*.pt. or (literature review or meta analysis or systematic review).ti,pt,ab,sh. or ((pool* or combined or combining) adj2 (data or trials or studies or results)).ti,ab. or (peto or dersimonian or der simonian or fixed effect).tw,sh. or (retraction of publication or retract* publication or retract* publish*).pt. |
| ☐ | 8 | 4 or 5 or 6 or 7 |
| ☐ | 9 | 3 and 8 |
| ☐ | 10 | 9 not ((exp animal/ or nonhuman/) not exp human/) |

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile1.pdf