RESEARCH PROTOCOL – June 2003

The clinical and cost-effectiveness of once daily versus more frequent use of same potency topical corticosteroids for people with atopic eczema.

A. **Final version.**

B. **Details of review team**

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C. **Full title of research question**

The clinical and cost-effectiveness of once daily versus more frequent use of same potency topical corticosteroids for people with atopic eczema.

D. **Clarification of research question and scope**

- The terms atopic eczema and atopic dermatitis are used synonymously. In this review we will use the term atopic eczema (unless citing directly from the published literature), which is more commonly used in the UK.
- Atopic eczema is a multi dimensional phenomenon, and there are variations in the criteria used for diagnosis of the condition. This review will employ the diagnostic criteria set out by Williams et al (1994), for general guidance. However, as these criteria have only recently been applied in trials diagnostic criteria reported by included studies will be described.
- For the definition of disease severity (i.e. subsets of atopic eczema) there are a number of scoring systems which have been used to categorise disease into mild, moderate or severe disease (e.g. SCORAD). None of these scoring systems are accepted as a 'gold standard' and there is uncertainty and debate over their use. Where studies which have employed severity scoring systems are referenced in this review the scoring system will be stated, and guidance given as to the nature of the scoring system.
- Topical corticosteroids are the mainstay of treatment for atopic eczema. The BNF (45, March, 2003) lists, under topical corticosteroids for eczema (section 13.4), more than 50 products (comprising over 80 different preparations/formulations), from over 20 manufacturers. Some products have added ingredients (e.g. salicylic acid or antimicrobials), and there are a number of products which are available over-the-counter (OTC).
- This review will include topical corticosteroids reported in section 13.4 of the BNF (March, 2003), excluding compound preparations (i.e. antimicrobials, preparations containing added ingredients).

- Where included studies report on the clinical and cost-effectiveness of OTC products, findings will be presented separately; such products do not incur NHS expenditure, and their use is not generally under the direct guidance of a clinician.
- Topical corticosteroids are classified according to their potency, or strength, and are mild, moderate, potent or very potent. In this review we will use the classification of potency for each preparation as listed in the BNF (45).
- Most products are recommended for use 1-2 times daily (BNF), however, the frequency of application seems to have developed empirically (Lagos & Maibach, 1998) and twice daily application is the most common approach. This review will compare the use of topical corticosteroids once daily with more frequent use of products of the same potency.
- Early appraisal of some literature in this area indicates that the evidence-base, from randomised controlled trials/controlled clinical trials, comparing topical corticosteroids of the same potency is concentrated on products that are either potent or very potent (Hoare et al, 2001), whilst a large proportion of the patient group (60-70%) are expected to be treated with mild or moderate potency products.

E. **Report methods**

- The review will be undertaken as exhaustively as time allows following the general principles outlined in NHS CRD Report 4 (2nd Edition).
- This research protocol may be updated as the research programme progresses. Any changes in the protocol will be notified to the NCCHTA and NICE.

Search strategy

- Electronic databases that will be searched include: Cochrane Systematic Reviews Database; Cochrane Controlled Trials Register; NHS CRD (University of York) databases (including DARE, NHS EED and HTA database); Medline (Ovid); EMBASE; National Research Register; Science Citation Index; BIOSIS; EconLit; MRC Trials database; Early Warning System; and Current Controlled Trials. These will be searched for the periods covered by the databases, and will be limited to English language. See search strategy in Appendix a.
- Bibliographies of included studies and other related papers will be assessed for relevant studies.
- Experts will be contacted for advice and peer review, and to identify additional published and unpublished references and any ongoing studies.
- Industry submissions to NICE will be checked for the completeness of ascertainment of our searches.

Inclusion and exclusion criteria

Intervention

- Studies comparing once daily versus more frequent application of topical corticosteroids of the same potency will be included. Studies comparing corticosteroids with different potencies will be excluded. The review will include topical corticosteroids reported in section 13.4 of the BNF (March, 2003), excluding compound preparations (i.e. antimicrobials, preparations containing added ingredients).

Participants

- The review will include children and adults with atopic eczema (atopic dermatitis). Patients with other types of eczema such as contact dermatitis, seborrhoeic eczema, varicose eczema and discoid eczema will be excluded from the review. The review will use as a general guide the diagnostic criteria for atopic eczema set out by Williams et al (1994). Where uncertainty exists over the classification of disease in published studies, a clinical advisor will determine the appropriateness of the inclusion of the study in the review.

Design

- Systematic reviews and meta-analyses of RCTs as well as individual RCTs will be included. The review will consider products by potency grouping and where no RCT evidence is identified for a potency group the inclusion of controlled clinical trials (with concurrent controls) will be considered. Reports published only as abstracts and non-English language studies will be excluded. Published abstracts that would otherwise meet the inclusion criteria will be listed for information.

Outcomes

- Studies will be included if they report one or more of the following as primary outcomes; overall response to treatment (e.g. using severity scores), impact on clinical features of the condition (e.g. erythema, induration, pruritus, excoriation, thickening), relapse/flare-up rate, side-effects, compliance, tolerability, patient preference measures, and quality of life.

Inclusion and exclusion criteria will be applied by one reviewer and checked by a second. Any disagreement will be resolved through discussion.

Inclusion criteria for papers on cost-effectiveness

- All studies that present findings on the cost-effectiveness of once daily versus more frequent application of topical corticosteroids of the same potency will be included. Studies comparing products with other active ingredients (e.g. antimicrobials) will be excluded.

Data extraction strategy

- Data extraction will be undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved though discussion. A draft data extraction form is attached (Appendix a), but is subject to change.

Quality assessment strategy

- The quality of included systematic reviews will be assessed using criteria recommended by NHS CRD (university of York) (Appendix b).
- Quality assessment of RCTs will be undertaken in accordance with chapter II.5 of CRD Report 4 (2nd Edition) (Appendix c).
- Quality criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved though discussion.
- The quality of economic evaluations will be assessed for their internal validity (i.e. methods used), and external validity (i.e. the generalisability of the economic study to the population of interest), using the format recommended and applied in the CRD NHS Economic Evaluation Database (see details on: http://www.york.ac.uk/inst/crd/index.html).

Methods of analysis/synthesis

- The clinical effectiveness will be synthesised through a narrative review with tabulation of results of included studies.
- Data will be combined statistically if of sufficient quantity, quality and if sufficiently similar by meta-analysis using Review Manager Software.

Methods for estimating qualify of life, costs and cost-effectiveness and/or cost/QALY

- The costs and effects associated with once daily versus more frequent application of topical corticosteroids will be considered as part of this review.
- Published cost-effectiveness studies will be reviewed in detail, comprising a narrative review with a tabulation of results where appropriate. Cost-effectiveness studies will be identified as part of the search strategy documented above. Initial indications are that there are very few cost-effectiveness studies reporting on the comparison of topical corticosteroids (i.e. frequency of application) in atopic eczema.
- A cost-analysis will be undertaken to inform on the resource use and cost-consequences associated with the comparison of once daily versus more frequent application of products of the same potency. Costs will be obtained from the published literature, NHS sources and industry submissions where applicable. Costs to be considered will include the costs associated with treatment, and those NHS costs related to a difference in patient experience with respect to the comparison of treatment regimes (e.g. treatment of adverse events where a significant difference is identified). The perspective of the economic analysis will be that of the NHS and Personal Social Services Decision-Maker.
- Cost-effectiveness analysis will compare once daily versus more frequent application of topical corticosteroids (same potency), on the basis of the primary outcome measures specified above (e.g. response to treatment, relapse rate, impact on clinical features), and additional quality of life outcomes where documented as part of the literature review. Where clinical effect/outcomes are the same for both treatment regimes, the analysis may be limited to a cost-minimisation analysis.
- Where data are available an economic model will be constructed by SHTAC, using best available evidence, to synthesise the evidence on effectiveness of treatments and their associated costs, to determine cost-effectiveness in a UK setting. Where cost-effectiveness models have been reported in the literature in the area of atopic eczema (i.e. topical corticosteroids versus tacrolimus ointment), summary cost-effectiveness results have been presented as cost per disease-controlled-day (e.g. Ellis et al, 2003). However, where possible cost-utility estimates in terms of cost per QALY will be pursued and presented.
- The robustness of the results to the assumptions made in the cost analysis and the cost-effectiveness model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

F. **Handling the company submission(s)**

- SHTAC methods for reviewing the literature on cost-effectiveness/cost-utility, and for the cost-effectiveness analysis to be undertaken, are stated above.
- Industry submissions will be checked for additional studies that meet the SHTAC inclusion criteria, for data on costs, and for data on the current use of topical corticosteroids for atopic eczema in England and Wales.
- Results of cost-effectiveness analyses from industry will be compared with the SHTAC analysis, but this will not be a line by line critique of sponsors' models.
- Any ‘commercial in confidence’ data taken from the industry submissions will be clearly marked (underlined) in the report submitted to NICE. A separate version with any such data removed will also be submitted.

G. **Project management**

a. **Timetable/milestones** - submission of:

Draft protocol to NCCHTA: 30/05/03
Progress report: 22/09/03
Draft report to external reviewers and the NICE Technical Lead: 13/10/03
Assessment Report: 27/11/03

b. **Competing interests**
None known.

c. **External reviewers**:
The Technology Assessment Report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the TAR Team encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking which we will hold on file. Comments from external reviewers and the Technical lead, together with our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

H. **Appendices**

a. Draft search strategy (MEDLINE example)
b. Data extraction forms (RCTs and systematic reviews)
c. Quality Assessment Scale for Systematic Reviews
d. Quality Assessment Scale for RCTs
e. Background

Appendix a
Draft Search Strategy, Example: MEDLINE Database
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1 Skin Diseases, Eczematous/ (33)
2 exp Eczema/ (5071)
3 Dermatitis/ (4301)
4 Dermatitis, Atopic/ (7536)
5 eczema.ti,ab. (5436)
6 excema.ti,ab. (7)
7 1 or 2 or 3 or 4 or 5 or 6 (18207)
8 dermatitis.ti,ab. (19796)
9 7 or 8 (31027)

10 hydrocortisone.ti,ab,rw. (46275)
11 Hydrocortisone, Topical/ (940)
12 Hydrocortisone/ (42789)
13 beclamethasone.ti,ab. (12)
14 beclomethasone.ti,ab,rw. (2539)
15 Beclomethasone/ (2146)
16 exp Betamethasone/ (4264)
17 betamethasone.ti,ab,rw. (4400)
18 Clobetasol/ (560)
19 clobetasol.ti,ab,rw. (642)
20 clobetasone.ti,ab,rw. (101)
21 Desoximetasone/ (45)
22 desoximetasone.ti,ab,rw. (62)
23 Diflucortolone/ (36)
24 diflucortolone.ti,ab,rw. (89)
25 Fluocinolone Acetonide/ (900)
26 fluocinolone.ti,ab,rw. (977)
27 Fluocinonide/ (140)
28 fluocinonide.ti,ab,rw. (206)
29 Fluocortolone/ (241)
30 fluocortolone.ti,ab,rw. (281)
31 fluticasone.ti,ab,rw. (1102)
32 Halcinonide/ (37)
33 halcinonide.ti,ab,rw. (69)
34 mometasone.ti,ab,rw. (192)
35 Triamcinolone Acetonide/ (2616)
36 triamcinolone.ti,ab,rw. (4882)
37 alclometasone.ti,ab,rw. (30)
38 dioderm.ti,ab. (3)
39 efcortelan.ti,ab. (4)
40 mildison.ti,ab. (0)
41 locoid.ti,ab. (27)
42 modrasone.ti,ab. (1)
43 propaderm.ti,ab. (4)
44 betacap.ti,ab. (2)
45 betnovate$.ti,ab. (30)
46 bettamousse.ti,ab. (1)
47 diprosone.ti,ab. (16)
48 dermovate.ti,ab. (39)
49 eumovate.ti,ab. (11)
50 stiedex.ti,ab. (0)
51 nerisone.ti,ab. (8)
52 haelan.ti,ab. (5)
53 synalar.ti,ab. (44)
54 metosyn.ti,ab. (11)
55 ultralanum.ti,ab. (7)
56 cutivate.ti,ab. (4)
57 halciderm.ti,ab. (2)
58 elocon.ti,ab. (2)
59 hydrocal.ti,ab. (3)
60 calacort.ti,ab. (0)
61 dayleve.ti,ab. (0)
62 notisone.ti,ab. (0)
63 corteze.ti,ab. (0)
64 hydrocortisyl.ti,ab. (1)
66 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 64 (58245)

67 steroid$.ti,ab. (103850)
68 corticosteroid$.ti,ab,hw,rw. (38508)
69 glucocorticosteroid$.ti,ab,hw,rw. (1735)
70 glucocorticoid$.ti,ab,hw,rw. (45546)
71 Anti-Inflammatory Agents, Steroidal/ (9423)
72 Adrenal Cortex Hormones/ (28775)
73 67 or 68 or 69 or 70 or 71 or 72 (187517)

74 66 or 73 (225038)
75 7 and 74 (1921)
76 9 and 74 (2750)
77 limit 75 to human (1832)
78 limit 77 to english language (1214)
79 limit 76 to human (2595)
80 limit 79 to english language (1844)

Appendix b – Data extraction forms

Data extraction form for primary studies

Reviewer:		**Date:**	**Version:**
Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Study Ref: Author: Year: Country: Study design: Study setting: Number of centres: Funding:	Comparisons of different Interventions: 1. 2. Potency: Duration of treatment: Other interventions used:	Number of Participants: Sample attrition/dropout: Inclusion/exclusion criteria for study entry:	Primary outcomes: Secondary outcomes: Method of assessing outcomes: Length of follow-up:

Characteristics of participants:

	Once daily	**Twice daily / other**	**P Value**
Age			
Sex			

Results

Outcomes	**Once daily**	**Twice daily / other**	**P Value**
Comments			
Comments			
QoL			
Comments			
Comments			
Adverse Effects			
Comments			
Resource Use			
Comments			

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups:
- Blinding:
- Comparability of treatment groups:
- Method of data analysis:
- Sample size/power calculation:
- Attrition/drop-out:

General comments

- Generalisability:
- Outcome measures:

Reviewer:		Date:	Version:
Reference and Design	**Intervention**	**Participants**	**Outcome measures**
• Inter-centre variability: • Conflict of interests:			

Data extraction form for Systematic Reviews

Reviewer:	Date:	Version:
Reference	**Methods**	
Study Ref: Author: Year: Country: Study design: Study setting: Funding:	Aim/Objective: Search strategy: databases searched Inclusion criteria. *Interventions:* *Participants:* *Outcome measures:* *Study design:* Quality criteria: Application of methods: Methods for analysis	
Results Quantity and quality of included studies Treatment effect Economic evaluation Conclusions Implications of the review		
Methodological comments • Search strategy • Participants • Inclusion/exclusion criteria • Quality assessment of studies • Method of synthesis General comments • Generalisability • Funding		

Appendix c – Quality assessment for systematic reviews

Quality Assessment for Systematic Reviews	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	
2. Is there evidence of a substantial effort to search for all relevant research?	
3. Is the validity of included studies adequately assessed?	
4. Is sufficient detail of the individual studies presented?	
5. Are the primary studies summarised appropriately?	

Appendix d – Quality assessment for primary studies

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	

Appendix e - Background

Disease/Condition

- Atopic eczema (atopic dermatitis) is a chronic relapsing condition, characterised by frequent flare-ups on the skin (patches of red, dry, scaly and itchy skin), and treatments are aimed at symptom relief and the prevention of complications (e.g. infections), until remission occurs. It is a common inflammatory skin disorder with a reported prevalence of 15-20% in children and 2-10% in adults. For unclear reasons the prevalence of atopic diseases, including eczema, has risen steadily over the past 30 years (Friedman, 1998).
- Atopic eczema most commonly begins in infancy, with 65% of cases presenting before the age of 6 months and 80% in the first year of life (Friedman, 1998); 60% of childhood cases of atopic eczema are clear and free from symptoms in early adolescence, but many such apparently clear cases are likely to recur in adulthood (Williams, 2000). Little is known about short- to medium-term fluctuations in disease activity, often no explanation can be found for a particular flare up. However, the strongest and most consistent factors which appear to predict more persistent atopic eczema are early disease onset, severe widespread disease in early life, concomitant asthma or hay fever and a family history of atopic eczema (Williams, 2000)
- Atopic eczema is a multi dimensional phenomenon, and as such there are some uncertainties over the definition and diagnosis of the condition. Building on earlier work on the clinical features of the condition a UK Working Party of 16 physicians developed the criteria presented in Table 1, for use in epidemiological studies (Williams et al, 1994). These criteria are now commonly used, they have been shown to have good repeatability, and have been validated in many different populations (Williams, 2000).

Table 1. The UK refinement of the Hanifin and Rajka Diagnostic Criteria for AD for use in epidemiological studies.

To qualify as a case of atopic dermatitis with the UK Diagnostic Criteria, the child must have:
An itchy skin condition in the last 12 months
Plus three more of:
(i) onset below the age of two years*
(ii) history of flexural involvement
(iii) history of a generally dry skin
(iv) personal history of other atopic disease**
(v) visible flexural dermatitis as per photographic protocol

* Not used in children under 4 years of age ** In children under 4 years, history of atopic disease in a first-degree relative may be included.

- Disease severity scores are commonly used to describe subsets of atopic eczema (i.e. mild, moderate, severe disease). Such scoring systems aggregate scores (which are determined by a trained researcher or health professional), from a range of symptoms/disease characteristics. For example, the Nottingham Eczema Severity Score (NESS) considers areas of chronicity, extent and intensity of disease, presenting a total score between 3 and 15, with higher scores reflecting increases in disease severity (i.e. 9-11=moderate, 12-15=severe), (Emerson et al, 2000).
- The severity distribution of disease has been reported in a community sample of children aged 1-5 years (n=290), with atopic eczema, as 84% mild, 14% moderate, and 2% severe (Emerson et al, 1998).

Treatment

- Treatment of atopic eczema is aimed at suppressing the symptoms of disease and controlling or preventing complications. Presently, treatment largely comprises emollients, soap substitutes, topical corticosteroids to suppress inflammation, antibiotics to treat bacterial infection, antihistamines (usually the older sedative varieties), and bandages (wet dressings, or impregnated bandages).

Topical corticosteroids

- Topical corticosteroids are the mainstay of treatment for atopic eczema.

- Corticosteroids act by suppressing various components of the inflammatory reaction. Potency is classified as mild, moderate, potent or very potent, and it is advised that the weakest steroid that controls the disease effectively should be used. The strength and type of steroid that is prescribed for atopic eczema depends on the age of the patient, the site of the skin affected, the severity of the eczema and the presence of infection.
- Topical corticosteroids are used for symptomatic relief when disease flare-ups occur. Guidelines from the British Association of Dermatologists (BAD, 2003) suggest that the use of topical corticosteroids should be limited to a few days to a week for acute eczema, and for periods of up to 4 to 6 weeks to gain initial remission for chronic eczema.
- Mild and moderate potency products are rarely associated with side-effects. Absorption through the skin can cause severe pituitary-adrenal-axis suppression and Cushing's syndrome, depending on the area of the body treated and the duration of treatment. Local side effects include (BNF 45):
    - Spread and worsening of untreated infection;
    - Thinning of the skin which may be restored over a period of time after stopping although the original structure may never return;
    - Irreversible striae atrophicae (bands of thin wrinkled skin, initially red but becoming purple and white) and telangiectasia (a permanent dilation of pre-existing blood vessels creating small focal red lesions);
    - Contact dermatitis;
    - Perioral dermatitis (an inflammatory papular disorder on the face of young women);
    - Acne at the site of application in some patients;
    - Mild depigmentation which may be reversible.
- Topical corticosteroids are available as water-miscible creams, which are suitable for moist or weeping lesions; ointments, which are chosen for dry, lichenified or scaly lesions; or lotions, which are appropriate for minimal application to large or hair-bearing areas or for exudative lesions. Absorption is increased by the use of occlusive dressings, but as this also increases the risk of side-effects they should only be used on a short-term basis for very thick areas of skin (BNF 45).
- Corticosteroids can remain in the stratum corneum for up to two weeks with occlusion or two days without occlusion. Absorption is a relatively slow process, therefore a single daily application may be effective (Lagos & Maibach 1998).
- Most patients require general use of emollients, which need to be applied as liberally and frequently as possible. Intensive use of emollients will reduce the need for topical steroids (BAD Guidelines, 2003).
- As discussed in Section D above, there are a large variety of topical corticosteroid products available for the treatment of atopic eczema. There is a lack of comparative data to help clinicians decide on what may be the best treatment option for their patient (Williams, 2002).
- Patients' fears about using topical corticosteroids may have implications for compliance with treatments. Fears are often based on a perceived risk of side-effects (e.g. skin thinning, systemic effects), which is much greater than the probability of the occurrence of side-effects (e.g. Charman et al, 2000, Williams, 2002). Issues related to patient fears surrounding use of topical corticosteroids should be considered in the assessment of treatment options.

Current Service Provision

- Most cases of atopic eczema are mild in severity and the large majority of patients with atopic eczema (over 90%) are treated in the community; referral to secondary care health services by GPs is infrequent (Emerson et al, 1998).
- Topical corticosteroids are generally recommended for application 1-2 times daily (although some products, e.g. mometasone furoate, Elocon®, are only recommended for once daily application). However, frequency of application has developed empirically and twice daily application of products is the most common treatment (Lagos & Maibach 1998).

Costs

- The mean cost per patient per year for topical corticosteroids is not large, circa £10-£15; however, due to large patient numbers the total costs for the NHS are very large.

- A small number of studies have estimated costs associated with atopic eczema. Emerson et al (2001) in a study involving children aged 1-5 years (n=290), estimate annual NHS costs (1995-6 cost presented) across the UK for atopic eczema in this patient group to be £47 million, with £30 million of this being NHS expenditure. The total mean disease cost, over the 12-month study period, was £79.59 per patient, with the total NHS cost per patient at £50.65 per year (£28.62 for NHS consultations, plus £22.02 for NHS prescriptions). Emerson et al estimate that NHS prescription costs for atopic eczema in those aged 1-5 years in the UK are £13 million, but less than 25% of the prescription costs are attributed by the authors to topical corticosteroids; the majority of the NHS prescribing costs (76%) for this patient group are on emollients and bath preparations.
- Herd et al (1996) extrapolate the findings from a study (n=155) in rural Scotland and present estimates of the total UK expenditure on atopic eczema, finding total expenditure could be £465 million; with £125 million of this falling on the NHS. Herd et al report an estimated mean annual cost in their sample of £97, of which £63 is attributed to treatments (prescriptions), with most (over 60%) of the expenditure on treatments/prescriptions being on items other than topical corticosteroids (e.g. emollients, bath additives, bandages).

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