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Draft Protocol for Technology Assessment Report HTA
15th March 2013

1. Cost-effectiveness of second eye cataract surgery

2. Name of TAR team and project 'lead'

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Dr Jonathan Shepherd, Principal Research Fellow, SHTAC.

3. Plain English Summary

A cataract is a clouding that develops in the lens of the eye which results in symptoms such as blurred or reduced vision. Cataracts are linked to ageing and are more common in people over 65. Other risk factors include smoking, alcohol, diabetes, and use of medical drugs such as corticosteroids. The main treatment for cataracts is surgical extraction. Surgery involves removal of the natural (crystalline) lens of the eye that has developed an opacification (cataract) and replacement with an artificial lens to restore clarity of vision. Cataract extraction is a common procedure and is beneficial to patients in improving their vision and ability to perform daily activities. Cataract is generally a bilateral condition (i.e. affecting both eyes) and surgery is generally performed on one eye at a time. It is currently standard practice for surgeons to offer surgery where a second eye cataract exists and the patient is symptomatic and wishes to proceed. Cataract extraction in the first eye is known to be cost-effective for health services, however, there is uncertainty about how cost-effective second eye cataract surgery is.

We propose to summarise the most up-to-date and highest quality evidence on the benefits, harms and costs of second eye cataract surgery in adults. We will search for, review and assess the quality of trials that examine how effective second eye cataract surgery is, compared with single eye cataract extraction. The review will be undertaken following a recognised, systematic and transparent approach, allowing people to understand and judge the process and methods we have used. We will summarise the findings of the review through a discussion and, if appropriate, by combining results statistically. We will develop an economic model either through adapting an existing model or developing a new economic model to examine the costs and benefits of second eye cataract surgery within the UK. The

model will use data from our review of trials, and data from recognised sources (e.g. national published data, data from local hospitals' finance departments), as well as advice from experts in the field. We will also identify the areas where further research is needed. The results of this study will be used to inform health policy and practice.

4. Decision problem

4.1 Research aim and objectives

The aim of this project is to assess the clinical effectiveness and cost effectiveness of second eye cataract surgery. The objectives are:

- To conduct a systematic review of studies assessing the clinical effectiveness of second eye surgery.
- To conduct an economic evaluation comprising: a systematic review of cost-effectiveness studies of second eye surgery; and to develop/adapt an economic model to estimate cost-effectiveness.

Cataract removal surgery is a common procedure in the UK and has been shown to be cost-effective in the initial eye.[1] Some patients with bilateral cataract may only have surgery on one eye, but it is suggested that surgery on the second eye may have additional benefit for patients in terms of improving vision and being able to perform everyday activities (e.g. being able to drive). However, there is debate about how cost-effective second eye surgery would be.

Scoping searches for this protocol have identified three published randomised controlled trials (RCTs) of second eye cataract surgery compared to first eye surgery.[2-4] All of these trials reported varying degrees of benefit associated with second eye surgery, in terms of improved visual acuity, visual symptoms, and quality of life. No published systematic reviews of the clinical effectiveness and cost effectiveness of second eye cataract surgery have been identified. Three published economic evaluations have been identified[5-7] (one of which was a trial-based evaluation conducted in the UK[5]) which have used divergent methods and generated mixed results (see section 6). An evidence synthesis and economic evaluation would therefore be useful to inform health service policy and practice in this area.

4.2 Background

A cataract is a clouding that develops in the crystalline lens of the eye which results in symptoms such as blurred or reduced vision, and problems associated with glare or low-contrast conditions. Formation of cataracts is linked to ageing, with the gradual accumulation of yellow-brown pigment within the lens reducing light transmission. Cataracts can also be congenital or secondary to other causes (e.g. chronic uveitis). Other, extrinsic, risk factors include smoking, alcohol diabetes, and use of systemic corticosteroids. In developing countries malnutrition and acute dehydrating diseases are also associated with cataract development.[8]

Cataracts are a common cause of visual impairment worldwide, and are more common in older people. The North London Eye Study randomly sampled people aged over 65 years from general practices in north London (1547/1840 responding), and found a prevalence of cataract causing visual impairment (visual acuity in one or both eyes poorer than 6/12, attributable to lens opacity) of 30%.[9] The prevalence of cataract increased steadily with age from 16% in the 65 to 69 age group, to 71% in people aged over 85 years. In the MRC Trial of Assessment and Management of Older People in the Community, nurses tested visual acuity in 14,403 people aged 75 years and older from 49 general practices in Britain.[10] Of 976 people with binocular visual impairment (binocular acuity <6/18) excluding refractive error, 36% were classified as having cataract.

4.3 Definition of the intervention

Cataract extraction surgery is considered to be the only curative intervention available. First eye cataract surgery refers to removal of the cataract in only one eye. Second eye cataract surgery is performed in patients with bilateral cataract at a point in time following first eye surgery. Surgery involves removal of the natural (crystalline) lens of the eye that has developed an opacification (cataract) and replacement with a synthetic lens to restore clarity of vision.

Phacoemulsification is the standard method of cataract removal in the NHS and is associated with better visual outcome than conventional extracapsular surgery.[11] It involves making small incisions (e.g. 3mm in width) where the clear front covering (cornea) meets the white of the eye (sclera). A circular opening is created on the lens surface (capsule). A small surgical instrument (phaco probe) is inserted into the eye and ultrasound waves are used to break the cataract into small pieces. The cataract and lens pieces are removed from the eye using suction and an intraocular lens implant may then be placed inside the lens capsule. The procedure is usually carried out under local anaesthetic as day surgery.

4.4 Place of the intervention in the treatment pathway(s)

People with cataracts may be referred to an ophthalmologist by a GP or optometrist. Referral criteria include clinically significant visual symptoms related to the cataract (e.g. reduced visual acuity, functional impairment), negative effects on the patient's lifestyle by the cataract, and patient's wish to undergo surgery.

Cataract extraction is one of the most common elective surgical procedures in the UK. In 2009-10 there were 334,142 cataract extractions performed in England.[12] It is estimated that over a third of NHS cataract operations are performed in the second eye.[13] Patients are generally assessed for their second eye surgery at their first eye surgery post-operation check (e.g. four weeks post-operation). They then may wait up to a further 18 weeks for surgery unless there is an urgent reason to do it sooner. It is very uncommon for cataract extraction to take place in both eyes simultaneously due to the risk of associated complications including bilateral infective endophthalmitis (inflammation of the inside of the eye) which may lead to blindness in both eyes. Expert clinical opinion suggests that 1% or fewer extractions are simultaneous.

The indication for second eye surgery is based on whether the patient has a cataract in the second eye, is symptomatic and wishes to undergo surgery. Patients would have a glasses check so that they can assess the full benefit of the first eye surgery, in order to correctly judge their level of symptoms and visual rehabilitation with a change in glasses. The threshold for impairment to visual acuity would be the same as for initial cataract extraction surgery, and expert clinical opinion suggests that thresholds may vary between health trusts. A proportion of patients choose not to undergo second eye surgery and some die before they develop a second cataract.

The Royal College of Ophthalmologists cataract surgery guidelines (2010) state that it is clinically and economically appropriate for second eye surgery to be offered to those patients who want it. A 1b recommendation is given (recommendation based on at least one randomised trial).[13] Similarly, the Scottish Health Technologies Group issued an advice statement in September 2012 advising that there is RCT evidence to support second eye surgery and evidence from cost-utility analysis to demonstrate lifetime cost-effectiveness.[14] In England and Wales the National Institute for Health and Clinical Excellence (NICE) has not appraised second eye cataract surgery.

4.5 Relevant comparators

Single eye cataract surgery can be considered a relevant comparator in patients with bilateral cataracts not currently scheduled for second eye surgery. They may receive additional supportive care such as prescription glasses.

4.5 Outcomes

The clinical-effectiveness of cataract surgery can be measured in a variety of ways. Commonly used clinical visual measures include: visual acuity (clearness of vision measured via, for example, a Snellen chart); stereopsis (depth perception); contrast sensitivity (the ability to see objects that may not be outlined clearly or that do not stand out from their background) and stereoacuity (the smallest detectable depth difference that can be seen in binocular vision).

Functional status is measured using assessment tools including the visual functioning index (VF-14), a well-established patient questionnaire designed to measure functional impairment caused by cataracts. In the VF-14 patients rate their ability to undertake activities such as reading a newspaper or a book, driving and reading traffic signs or taking part in games, and a total score is computed representing the degree of visual function.[15] It is suggested, however, that the VF-14 is not sensitive to all cataract symptoms and therefore a new instrument to assess the impact of cataract surgery in terms of visual function and quality of life is needed.[16]

The health related quality of life of people with cataracts has been assessed in clinical trials using generic instruments such as the SF-36[2] and the Euroqol EQ-5D.[5] The EQ-5D has five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three possible levels of severity for each.

Like all forms of surgery, cataract removal is associated with adverse events. These can include: endophthalmitis; retinal detachment; bullous keratopathy (swelling of the cornea); and intraocular lens dislocation.

4.6 Population and relevant sub-groups

As discussed earlier, cataracts mainly affect older people, with increasing prevalence with age. Some people may have eye co-morbidities such as age-related macular degeneration or glaucoma.

5. Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical-effectiveness will be undertaken systematically following the general principles outlined in Centre for Reviews and Dissemination (CRD) report 'Undertaking Systematic Reviews of Research on Effectiveness' (Third edition)[17] and the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (formally QUOROM statement).[18]

5.1 Search strategy

A comprehensive search strategy will be developed, tested and refined by an experienced information scientist (see Appendix for draft Medline search strategy). Separate searches will be conducted to identify studies of clinical-effectiveness, cost-effectiveness, Health Related Quality of Life (HRQoL), resource use and costs, and epidemiology.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

Electronic databases to be searched will include:

- General health and biomedical databases – MEDLINE (Ovid); PreMedline In-Process & Other Non-Indexed Citations; EMBASE; the Cochrane Central Register of Controlled Trials; and the Science Citation Index.
- Specialist databases – the Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effectiveness (DARE); Health Technology Assessment database; EconLit; NHS Economic Evaluation Database.
- Grey literature and research in progress – UK Clinical Research Network Portfolio Database; and Conference Proceedings Citation Index –Science (Web of Science); Current Controlled Trials; Clinical Trials.gov; BIOSIS; NIHR Clinical Research Network Portfolio; CenterWatch; Health Services Research Projects in Progress and Computer Retrieval of Information on Scientific Projects (CRISP).

All databases will be searched from inception to the current date and searches will be limited to English language.

5.2 Inclusion/Exclusion criteria:

- Population: adults (aged 18 or over) who have had one cataract operation already and still have or develop significant cataract causing visual impairment in the other eye.
- Interventions: cataract surgery for the second eye. Studies reporting any surgical technique will be included.
- Comparators: cataract extraction surgery in one eye only.
- Outcomes: clinical visual measures (visual acuity; stereoacuity; contrast sensitivity); patient reported visual disability and symptoms (e.g. VF-14); patient satisfaction with surgery and vision; health related quality of life (e.g. EQ-5D); adverse events.
- Types of studies: Randomised controlled trials (RCTs) will be included. If necessary non-RCT data will be sought to inform the cost-effectiveness analysis (e.g. on safety). Any systematic reviews identified will be used only as a source of references.
- Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken.

5.3 Inclusion, data extraction and quality assessment process

Studies will be selected for inclusion through a two-stage process using the predefined and explicit criteria (as specified in section 5.2). The literature search results will be screened by two reviewers to identify all citations that may meet the inclusion criteria. Full manuscripts of relevant studies will be retrieved and assessed by two reviewers using a standardised eligibility form.

Data extraction and quality assessment will be undertaken by one reviewer and checked by a second reviewer using a pre-designed and piloted data extraction form to avoid any errors. At each stage, any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

5.4 Quality assessment

Included trials will be assessed in terms of their risk of bias (e.g. selection bias, detection bias, performance bias, attrition bias, and selective reporting bias) using Cochrane Collaboration criteria.[19;20] Aspects of study quality including statistical procedures, outcome measurement and generalisability will also be assessed.

5.5 Methods of analysis/synthesis

Studies will be synthesized through a structured narrative review with tabulation of results of included studies. Where appropriate and where suitable data are available, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes. The specific methods for meta-analysis and for the detection and investigation of heterogeneity will depend upon the summary measure selected and will used standard procedures recommended by the Cochrane Collaboration.[19] Cochrane Review Manager (RevMan) software will be used to perform any meta-analysis. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

6. Report methods for synthesising evidence of cost-effectiveness

The cost-effectiveness of second eye cataract surgery will be assessed through two stages: a systematic review of cost effectiveness studies and the development of a decision analytic economic model.

6.1 Review of published cost-effectiveness studies

The sources detailed in section 5.1 will be used to identify studies of the cost effectiveness of second eye cataract surgery. Studies will be included in the systematic review of cost-effectiveness if they are full economic evaluations (cost effectiveness, cost utility or cost benefit analyses) that report both measures of costs and consequences. The methodological quality of included studies will be assessed using accepted criteria for appraising economic evaluations.[21] Where relevant this will be supplemented with additional criteria for critical appraisal of model-based evaluations.[22] Studies will be synthesised through a narrative review that includes a clear explanation of the assessment process, detailed critical appraisal of study methods, critical assessment of data used in any economic models and tabulation of the results of included studies. Published studies conducted in the UK and adopting an NHS and Personal Social Services (PSS) perspective will be examined in more detail. Stand alone cost analyses based in the UK NHS will also be searched for – these will not be included in the systematic review, but will be retained as sources of information on resource use and cost associated with second eye cataract surgery (including short term and longer term adverse events).

Scoping searches have identified two published cost utility studies of second eye cataract surgery,[5;7] in addition to the one study identified in the NIHR HTA Programme commissioning brief, by Busbee and colleagues.[6] One of the additional studies was conducted in the UK and has an NHS and Personal Social Services (PSS) perspective.[5] Neither of the additional studies is a model-based evaluation – one was a study of "routine" cataract surgery (of 219 patients, 73 had both eyes operated on and 59 had a second eye operation, the first eye having been operated earlier)[7], the other was conducted alongside an RCT.[5]

6.2 Evaluation of costs and cost-effectiveness

Existing economic models developed to estimate the cost-effectiveness of second eye cataract surgery, identified in the systematic review of economic evaluations, will be assessed for their quality, relevance and suitability for adoption in the current review. If considered relevant and valid the models will be adapted (if required) and populated with updated (and UK-practice-relevant) clinical and cost parameter values using data identified in our clinical and cost effectiveness reviews.
The decision tree model presented by Busbee and colleagues,[6] will be considered for adaptation in this economic evaluation. Key assumptions of this study will be discussed with our clinical and methodological advisors for their appropriateness. These include:

- the inclusion and timing of adverse events: endophthalmitis; cystoid macular edema; lost lens fragments (each occurring within 4 months of surgery); posterior capsular opacification (occurring at rate of 28% over 5 years, with treatment occurring on average 2 years after surgery); retinal detachment (in 0.81% of cases, with treatment on average 1 year after surgery); intraocular lens dislocation (in 1.1% of cases); and pseudophakic bullous keratopathy (in 0.3% of cases, with

treatment on average 1 year after surgery). Retinal detachment following posterior capsular opacification was assumed to occur in 3% of cases.

- the most appropriate measure of outcome. The model uses assumed levels of bilateral visual acuity which are then mapped to utility values derived using the time-trade- off technique. However, it is recognised that bilateral visual acuity may have limitations and other measures, including patient-reported visual dysfunction, may be more informative.

Current guidelines for good practice in decision-analytic modelling and the general principles outlined in the NICE 'reference case' will be followed.[22-24] Development of the structure and parameters of the model will be informed by several sources including previous models identified in the systematic review of cost effectiveness, evidence from our systematic review of clinical effectiveness, as well as guidance from clinical and methodological advisors. The model will be validated through discussion with expert advisors. Additional targeted literature searches will be required to populate other parameters in the model as necessary.

The model will adopt a UK NHS and PSS perspective with cost and outcomes discounted at an annual rate of 3.5%. The model will present estimates of the cost effectiveness of second eye cataract surgery, in terms of incremental cost per quality adjusted life year (QALY) gained, compared with first-eye surgery only.

Resource use for second eye cataract surgery, including management of adverse events, will be estimated from studies included in the systematic review of clinical effectiveness, published costing studies identified by our searches, any relevant clinical guidelines and from discussion with expert advisors. As far as is possible costings developed for the model will proceed by first identifying and quantifying resource use and then applying appropriate unit costs. Where resource use data from published literature is insufficient we would use estimates from relevant clinical experts and this will be clearly identified in the final report. To develop unit cost estimates we will assess official, nationally-representative sources (NHS Reference Costs,[25] Unit Costs of Health and Social Care,[26] British National Formulary[27]) for applicability and level of detail, as well as unit cost estimates applied in studies included in the systematic review of cost effectiveness and in costing studies identified by our searches. If these sources are inadequate we would develop unit cost estimates in collaboration with the costing unit at Southampton University Hospitals NHS Trust. Costs will be inflated to current prices using the Hospital and Community Health Services Pay and Prices Index, where necessary.[26]

Health-related quality of life (HRQoL) data, where available, will be extracted from studies included in the clinical- and cost-effectiveness systematic reviews. Where available, the impact of treatment adverse effects on patients will also be incorporated. Where QoL data are insufficient to calculate utility estimates, data will be derived from the broader literature or estimated from other sources. In accordance with the NICE methodological guide for technology appraisals,[24] the utility values used in the model will be elicited where possible from the general population using a preference-based method. Where these are not available, utility estimates will be derived from alternative sources and the assumptions made will be explicitly stated.

The cost-utility studies identified in our preliminary searches vary in the approaches used to estimate the utility gain associated with second eye cataract surgery. Busbee and colleagues[6] estimated levels of bilateral visual acuity (they assumed the same utility values based on VA outcomes for patients having first-eye surgery) and mapped these to previously estimated utility values associated with given levels of bilateral visual acuity. This yielded comparatively large utility gains of 0.109. In contrast, the other studies based their utility estimates on patient responses to generic HRQoL instruments (EQ-5D[5] and 15D[7]) valued using population-derived tariffs. These both estimated substantially lower utility gains following second-eye surgery (a small QALY gain of 0.015 for a 12 month time horizon [difference in EQ-5D utility at post-surgery follow-up not reported] in one study[6] and a statistically non-significant decrease of -0.01 in the other[7]). Both studies using patient-reported QoL measures included patients with limited vision loss (Sach and colleagues[5] report that 86% of trial participants had baseline visual acuity of 6/12 or better, while Rasenen and colleagues[7] noted that 17% of patients reported having no

preoperative difficulty in seeing and 47% only minor difficulties). It is not clear how far differences in patient populations studied may have given rise to divergent results in these studies, although baseline visual dysfunction (in the eye to be operated on) is likely to be an important factor in determining the potential gain from second eye surgery. Current Cataract Surgery Guidelines published by the Royal College of Ophthalmologists[13] note potential benefits from second eye surgery, but do not indicate the degree of visual dysfunction in the second eye at which it would be appropriate to undertake second eye surgery.

Sensitivity analyses and scenario analyses will be conducted with respect to variables over which there is greatest uncertainty. For the deterministic analyses this will be oriented toward variables with the greatest uncertainty over their methods of derivation or where choices/ judgments have had to be made between alternative sources. The key variables to be explored in sensitivity/ scenario analyses are likely to be the clinical benefit (for example gain in bilateral visual acuity) from second eye cataract surgery and the utility associated with such benefits. However the robustness of model results to other clinical variables (including incidence and timing of adverse events) and to resource use assumptions will also be considered. The importance of the underlying model assumptions will be assessed through an analysis of different scenarios, particularly where evidence to populate the model is inadequate or conflicting (for example where the model uses data derived using expert opinion). The results of the probabilistic sensitivity analysis will be presented using cost effectiveness acceptability curves (CEACs).

7. Expertise in this TAR team

SHTAC is one of nine academic research teams in the UK contracted to the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme to assess the clinical and cost-effectiveness of health technologies. Our research supports several key decision making bodies within the UK, including the National Institute for Health and Clinical Excellence (NICE). With expertise in evidence synthesis, health economics, statistical modelling and epidemiology, SHTAC is involved in research addressing major policy questions on the use of drugs, devices, procedures, screening programmes, health promotion and public health, and other interventions. SHTAC has previously conducted research into eye diseases, including a systematic review and economic evaluation of ranibizumab and pegaptanib for age-related macular degeneration.[28;29]

Advisory group

An advisory group has been recruited comprising clinical experts in ophthalmology, experts in health technology assessment methodology (including health economics) and representatives from patient organisations. The group will has commented on the draft protocol and will comment on the draft final report. The group will be consulted during the course of the project for advice as necessary. The current members of the group are:

- Professor Janet Marsden, Professor of Ophthalmology and Emergency Care & Chair of the RCN Ophthalmic Nursing Forum, Research Institute for Health and Social Change (Health Care Studies Department), Manchester Metropolitan University.
- Professor John Sparrow, Consultant Ophthalmologist, University Hospitals Bristol NHS Foundation Trust, & Honorary Professor of Ophthalmic Health Services Research and Applied Epidemiology, University of Bristol.
- Mr Simon P Kelly, Chair of Quality & Safety sub-committee of the Royal College of Ophthalmologists, & Consultant Ophthalmic Surgeon at Royal Bolton Hospitals NHS Foundation Trust.
- Dr Ewen Cummins, Health Economist, McMaster Development Consultants

Additional members may be recruited to the group during the course of the project, as required.

8. Competing interests of authors

None

9. Timetable/milestones

To follow

10. Appendices

10.1. Draft Medline (Ovid) search strategy

1 exp cataract extraction/ (26455)
2 (cataract* adj5 (surg* or remov* or extract* or procedure* or operat* or excis* or aspirat* or incis*)).tw. (19067)
3 phacoemulsification.tw. (5253)
4 (PKE or PCIOL or ECCE or ICCE or MSICS or MISICS or SICS).tw. (931)
5 (pseudoaphakia or pseudoaphakic or phakectomy or phakectomies or "enzymatic zonulolysis" or "zonulolyses enzymatic" or "enzymatic zonulolyses" or "zonulolysis enzymatic").tw. (107)
6 lens implantation, intraocular/ or lenses intraocular/ (16135)
7 "cataract patient*".tw. (1092)
8 or/1-7 (36944)
9 ("single eye*" or "right eye*" or "left eye*" or "one eye" or "dominant eye*" or "better seeing eye*" or "either eye" or "unilateral cataract*" or "first eye*").tw. (22936)
10 ("fellow eye*" or "second eye*" or "both eyes" or "other eye*" or "two eyes" or "next eye*").tw. (16331)
11 (eye* adj5 (sequential* or simultaneous* or serial*)).tw. (1275)
12 (bilateral* adj5 cataract*).tw. (1369)
13 8 and (9 or 10 or 11 or 12) (3749)
14 Randomized Controlled Trials as Topic/ (83981)
15 randomized controlled trial.pt. (339605)
16 controlled clinical trial.pt. (85425)
17 Controlled Clinical Trial/ (85425)
18 placebos/ (31477)
19 random allocation/ (76252)
20 Double-Blind Method/ (117819)
21 Single-Blind Method/ (16898)
22 (random* adj2 allocat*).tw. (18020)
23 placebo*.tw. (140190)
24 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (115464)
25 crossover studies/ (30752)
26 (crossover* or (cross adj over*)).tw. (51975)
27 Research Design/ (68167)
28 ((random* or control*) adj5 (trial* or stud*)).tw. (452653)
29 Clinical Trials as Topic/ (163152)
30 random*.ab. (567167)
31 or/14-30 (1175731)
32 13 and 31 (612)

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