Meniscal Transplantation and its Effect on Osteoarthritis Risk

AN ABRIDGED PROTOCOL FOR THE METEOR STUDY: A COMPREHENSIVE COHORT STUDY INCORPORATING A PILOT RANDOMISED CONTROLLED TRIAL

N. A. Smith, J. Achten, N. Parsons, D. Wright, B. Parkinson, P. Thompson, C. E. Hutchinson, T. Spalding, M. L. Costa

From University of Warwick, Coventry, United Kingdom

Objectives

Subtotal or total meniscectomy in the medial or lateral compartment of the knee results in a high risk of future osteoarthritis. Meniscal allograft transplantation has been performed for over thirty years with the scientifically plausible hypothesis that it functions in a similar way to a native meniscus. It is thought that a meniscal allograft transplant has a chondroprotective effect, reducing symptoms and the long-term risk of osteoarthritis. However, this hypothesis has never been tested in a high-quality study on human participants. This study aims to address this shortfall by performing a pilot randomised controlled trial within the context of a comprehensive cohort study design.

Methods

Patients will be randomised to receive either meniscal transplant or a non-operative, personalised knee therapy program. MRIs will be performed every four months for one year. The primary endpoint is the mean change in cartilage volume in the weight-bearing area of the knee at one year post intervention. Secondary outcome measures include the mean change in cartilage thickness, T2 maps, patient-reported outcome measures, health economics assessment and complications.

Results

This study is expected to report its findings in 2016.

Cite this article: Bone Joint Res 2015;4:93–8

Article focus

- The aim of this study is to aid a definitive evaluation of whether meniscal allograft transplantation is chondroprotective compared with standard treatment.
- It will assess the variability and distribution of the primary outcome measure, to inform a sample size calculation in a definitive evaluation.
- It will also identify issues with the trial study design including recruitment, retention, trial delivery and intervention fidelity.

Key messages

- It has not been definitively shown that meniscal allograft transplantation is chondroprotective, despite being scientifically plausible.
- This trial will provide the first high-level evidence testing the hypothesis that it may be chondroprotective in patients with a symptomatic meniscal deficient knee compartment.

Introduction

The menisci have important functions in the knee including load sharing and shock absorption; they also function as secondary stabilisers. Meniscal tears are the most common knee injury, with an incidence of 61 per 100 000 per year, equating to over 36 000 per year in the United Kingdom. Partial meniscectomy is the usual procedure performed in the symptomatic knee if the meniscus is not amenable to, or has had a failed, repair. Removal of part or all of the meniscus increases the stress on the knee articular cartilage, with one study showing a 75% reduction in knee joint contact area and increased peak contact pressures of 235%. It is well documented that (partial and total) meniscectomy increases the risk of
osteoarthritis (OA).\textsuperscript{6,7} with one systematic review showing a mean prevalence of 53.5% in patients that had undergone some form of meniscectomy, at a minimum of five-years follow-up.\textsuperscript{7}

Meniscal allograft transplantation is a well-recognised procedure for treatment of pain and swelling in a meniscus-deficient compartment of the knee.\textsuperscript{8} However, there has been very little research on human participants to assess its potential chondroprotective effect on articular cartilage.

Volumetric MR mapping of the change in knee cartilage has been shown to be highly sensitive with a very low error.\textsuperscript{9} It is also increasingly accurate, focusing analysis on the central weight-bearing areas of the articular surface within the knee.\textsuperscript{10} This study aims to provide the first high-level evidence testing the hypothesis that meniscal allograft transplantation is chondroprotective by comparing it with a non-operative personalised knee therapy programme.

Materials and Methods

Study design. This will be a comprehensive cohort study with an embedded pilot randomised trial. Therefore, there will be a randomised arm and a parallel non-randomised patient-preference arm. The study will be performed at a single centre in the United Kingdom (University Hospitals Coventry and Warwickshire NHS Trust (UHCW)). Recruitment to randomised operative versus non-operative trials is notoriously difficult due to strong patient preferences.\textsuperscript{11,12} Having a parallel patient preference group should improve recruitment and may provide a more precise estimate of effect size when analysed as a single cohort, due to a larger sample size. It will also give the study greater external validity as the overall rate of recruitment is anticipated to be significantly higher.\textsuperscript{13}

Study funding. This study has been supported by Arthritis Research UK as part of a Clinical Research Fellowship award (award number 20149).

Ethical approval. This study has been reviewed by the West Midlands – Solihull Research Ethics committee (Ref: 13/WM/0315). It was given ethical approval on the 3 October 2013. The study will be carried out in compliance with the Helsinki Declaration.

Study registration. This study has been registered with the International Standard Randomised Controlled Trial Number Register (ISRCTN14194954) and the National Institute for Health Research Comprehensive Research Network (CRN) Portfolio (UKCRN ID15557).

Timeline. The study started recruiting on the 28 November 2013 and will be open for one year. Follow-up will be complete at one year following the start of the intervention in the last patient.

Study participants. Patients between the ages of 16 and 50 years with a symptomatic, meniscal-deficient compartment of the knee, in which the treating surgeon believes that the patient may benefit from meniscal allograft transplantation, will be included. These broad and pragmatic criteria should ensure that the results of this study can be generalised to the wider population of patients with a symptomatic meniscal-deficient knee compartment.

Symptoms in the knee include pain, swelling or stiffness and can be present intermittently to be eligible. The amount of meniscal deficiency is difficult to accurately quantify. Therefore, it is left to the treating surgeon to decide whether there is enough meniscal deficiency (loss) that the patient may benefit from meniscal allograft transplantation. The following guidance will be used in the decision-making process: a deficient meniscal rim providing no circumferential fibre support or an intact rim of less than 2 mm width over the majority of the meniscus. Meniscectomy due to trauma is likely to be the most common reason for meniscal deficiency. However, other meniscal pathologies would be eligible, for example previous excision of a discoid meniscus.

Patients will be excluded if they have had previous cartilage modifying procedures such as autologous chondrocyte implantation or have significant exposed subchondral bone in the affected compartment due to arthritis (diagnosed on previous arthroscopy or MRI scan), as these factors would confound the assessment of the articular cartilage in the study. Patients that have contraindications to anaesthetic, as well as those who show evidence that they would be unable to adhere to trial procedures, will also be excluded.

Recruitment. Patients will be recruited from elective knee clinics at University Hospitals Coventry and Warwickshire NHS Trust. Once an eligible patient is identified by the treating surgeon, they will be referred to a research fellow or research associate.

Consent. The patients will be informed about the randomised controlled trial (RCT) group and given a patient information sheet (PIS) specific to the RCT. If patients are unwilling to have their treatment allocation decided by randomisation, they will be given the opportunity to be part of the patient-preference follow-up group. A second PIS, which gives information about this follow-up group will be given to patients. These participants will be allowed to decide their treatment allocation and will have their data collected as part of a ‘follow-up-only’ group. They will, therefore, not have MRI scans at four and eight months. Potential participants will be offered as much time as they require to consider the study. They may withdraw from the study at any time without prejudice.

Randomisation. This will be by a computer-generated sequence and a 1:1 allocation, stratified for ipsilateral limb malalignment. The Warwick Clinical Trials Unit secure telephone randomisation service will be used to provide the participant allocation once the patient has
consented to take part in the study. The allocated treatment will then be reported back to the chief investigator and the treating surgeon.

**Blinding.** The participants cannot be blind to their treatment. The treating surgeons will of course not be blind to the treatment, but will take no part in the post-operative assessment of the participants which will be performed by a research associate blinded to the treatment allocation. The MRI volume analysis will be performed by IMorphics Ltd (Manchester, United Kingdom), an independent medical image analysis company who will also be blinded to the treatment allocation. The statistical analysis will also be performed blind to the participants' treatment.

**Study interventions**

**Operative group.** Participants will usually have a general anaesthetic and femoral nerve block, but the attending anaesthetist will make the final decision based on the patient's clinical requirements. Participants will be in a supine position with a thigh side support. The surgery will be performed by one of the knee surgeons competent in meniscal transplantation and osteotomies. There will be no learning curve effect in this study as all participating surgeons performing the operations are proficient and experienced in the procedures.

The meniscal allograft is fresh–frozen and sourced from one of two tissue banks: NHSBT Tissue Services, (Liverpool, United Kingdom), or Allosource USA, (Denver, Colorado, imported by Fannin UK, Dublin, Ireland). These sources have been regularly used for meniscal transplantation as standard practice at UHCW NHS trust. The lack of availability from any one source requires that more than one source is used. The meniscal allograft is dissected from the tibial bone block marking the topographical orientation. Number two non-absorbable sutures are inserted in the anterior and posterior horns using a Bunnell type stitch and an absorbable middle traction suture is inserted at the anterior aspect of the popliteal hiatus laterally or at a point 40 mm from the posterior horn medially.

Surgery is performed using an arthroscopic technique. The procedure starts with a full assessment of the knee surfaces and the remaining amount of meniscal tissue. A 2 mm meniscal rim of tissue is maintained where possible. The meniscal bed is prepared to a fresh vascular margin before insertion of the allograft. Anterior and posterior meniscal root attachments are located and prepared using a shaver and rasp to expose bleeding bone. Guide wires are drilled from the anterior tibia to the insertion sites, maintaining a bone bridge on the tibia between the tunnels, and the guide wires are then over drilled to create 4.5 mm tibial bone tunnels. Lead sutures are inserted through the tunnels and are retrieved through the arthroscopic portal.

The meniscal allograft sutures are fed through the lead sutures and the allograft is ‘parachuted’ into place with the assistance of the middle traction suture. Fixation of the meniscal roots is achieved by tying the anterior horn and posterior horn lead sutures over the bone bridge on the anterior tibia. The meniscal rim is secured by placing multiple vertical stacked mattress sutures around the anterior two thirds of the meniscus with an inside-out technique. The posterior third of the meniscus is secured with all inside fixation devices, such as the Fast-Fix 360 (Smith and Nephew, Andover, United Kingdom).

**Osteotomy.** Participants will be assessed for limb malalignment prior to randomisation, and then stratified accordingly. Participants in which the weight-bearing line falls greater than 5% from the centre of the tibial plateau, where 100% represents the total tibial plateau width, will be offered an osteotomy. A medial opening wedge high tibial osteotomy would be performed for a varus proximal tibia and a medial closing wedge distal femoral osteotomy would be performed for a valgus distal femur, subject to surgeon’s preference and participant factors. In these procedures the medial tibia or medial distal femur is exposed through a longitudinal incision and an oblique osteotomy fashioned using image intensifier guidance. The final position is then held using a titanium plate and screws.

**Rehabilitation.** All participants randomised into the operative group will receive a standardised written programme of physiotherapy for their post-operative rehabilitation. Post-operatively, participants will be advised to touch weight bear with crutches for six weeks, followed by progression to full weight bearing by eight weeks. Cycling exercises can commence at four weeks when 90° bend has been achieved. Strength work starts at three months and running is not allowed until nine months. Participants will be advised of the risks of participating in contact sports and encouraged not to return to these activities in the long term. Although there is no agreement in the literature on the post-operative rehabilitation protocols, this regime is broadly in line with other studies that have published their post-operative protocols. It has been used for the rehabilitation of over 140 patients following meniscal allograft transplantation in our institution.14

**Non-operative group.** Participants will have a personalised knee therapy course, specifically designed for patients with pain in a meniscus-deficient knee. The course will involve a personalised knee therapy programme working on quadriceps control and strength, along with a core-strengthening programme to be delivered over a minimum of three months. The initial assessment will be performed by a senior knee physiotherapist, who will give a written booklet of exercise prescription, an exercise diary and an instruction list of common exercises. If the participant wishes to continue physiotherapy nearer their home, for example if they are not local to the area, they
will be referred for continued physiotherapy at a local unit. They will be assessed at routine follow-up clinics every four months, where adjustments to the personalised knee therapy can be made.

Participants with malalignment that are randomised to the non-operative group will also be given a size-matched offloading knee brace.

**Fidelity of the interventions.** Patients’ treatments in both the operative and non-operative groups will be assessed for adherence to the trial protocols. In the operative group, the surgery and post-operative rehabilitation will be reviewed by the chief investigator and a surgeon that is not directly involved in the treatment of trial patients. In the non-operative group, the treatment adherence will be determined by a senior physiotherapist that is not directly involved in the treatment of trial patients. The type and extent of physiotherapy will be determined from responses to the physiotherapy case report form completed at follow-up appointments. Adherence to the surgical protocol will be determined from the operative note and pictures.

**Outcome measures.** The primary endpoint of the trial is the mean change in cartilage volume in the central weight-bearing portion of the affected compartment of the knee at one year following the intervention. Secondary endpoints are cartilage volume changes at four and eight months following the intervention. The central weight-bearing portion of the affected compartment will be identified using the methods by Williams et al. This method has been shown to reveal focal cartilage losses, even in the presence of minimal global cartilage changes. It is also thought to be more accurate than global cartilage measurement as the cartilage edges, which are difficult to define accurately, are trimmed. The cartilage segmentation will be semi-automated and analysed by IMorphics Ltd, an independent medical image analysis company that specialise in changes in knee biomarkers for OA. They use active appearance models of the knee, which allow precise measurements of articular cartilage and changes in bone shape. They have extensive experience in measuring cartilage and changes in bone shape in both observational and experimental trials.

Loss of cartilage was chosen as a surrogate marker for OA in the absence of long-term follow-up. Loss of cartilage is a cardinal feature of OA and an annual loss of 4% to 6% has been shown in patients with knee OA, which exceeds errors of precision. A number of studies have also demonstrated an inverse relationship between pain and volume of cartilage.

The secondary outcome measures will include the Knee Injury and Osteoarthritis Outcome Score (KOOS), Lysholm score, International Knee Documentation Committee score (IKDC) and complications. An economics analysis will be performed using the EuroQol EQSD-SL health utility score. The mean change in cartilage thickness, changes in bone shape and T2 cartilage mapping, will also be performed.

**Follow-up.** In the randomised group, the participants will have MRI scans at baseline, four, eight and 12 months. In the patient preference group, the participants will have MRI scans at baseline and at one year. All participants will complete questionnaires at all time points (baseline, four, eight and 12 months). The trial period will start from the start of the intervention, rather than the date of randomisation. Questionnaires collected before the start of treatment may be used as the baseline questionnaire if the treatment starts within four months of the questionnaire being collected. MRI scans will be done as close as possible to the start of the intervention. If an MRI scan was done for clinical reasons (and was performed using the correct protocol) before the intervention started, it may be used as the baseline scan, as long as the intervention starts within four months of the scan. Participants in the patient preference group will not have repeat baseline scans, as they are a ‘follow-up-only’ group.

In the first instance a research associate that is blinded to the treatment allocation will collect all functional outcome scores from the participant in person. If the participant misses the appointment or is not willing to attend, the outcomes pack will be sent out by post and the patient will be telephoned. If the research associate is unable to obtain this information within four weeks of the time point for collection, the information will be deemed missing. Further data will be collected at later time points as originally planned.

**Post-recruitment withdrawals and exclusions.** Participants may withdraw from the trial at any time. If participants decide to have a different treatment to which they were randomised, participants will be followed up wherever possible and data collected as per the protocol until the end of the trial. Participants may be withdrawn from the study by the chief investigator at any time if any safety concerns arise.

**Sample size.** There are no previously performed similar studies, thus there is no way of gaining a meaningful standardised effect size. This study will therefore be a pilot and no formal power calculation will be performed. The recruitment period will be 12 months and it has been estimated that 18 patients will be entered into the randomised arm of the trial, based on a 50% recruitment rate. We expect that the majority of patients that do not wish to be randomised will wish to be part of the parallel patient preference group. One of the important findings of this study will be recruitment, as it will give information on the feasibility of a full RCT and expected timescales. A sample size of 18 participants will provide some guidance as to the likely size of the treatment effect and will allow nuisance parameters such as the variability (standard deviation) in the primary outcome to be estimated with some precision.
These data will enable a sample size calculation for a full RCT to be determined.

**Statistical analysis.** The main analysis will investigate differences in the primary outcome measure, cartilage volume between the treatment groups (operative and non-operative) on an intention-to-treat basis, at 12 months post-intervention. As this is a pilot study, the main analysis will be exploratory in nature, the aim being to assess the size and direction of observed differences between the two treatment groups, and the variability and distribution of the outcome measures at each point of assessment (four months, eight months and 12 months). It is likely that the primary outcome will not be normally distributed, so a range of data transformations (e.g. cube root) will be tested to see if they improve the measurement properties. Baseline data will be summarised to check comparability between treatment arms, and to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent. This is a relatively small study, and so group means are unlikely to be estimated with much precision. However, the statistical significance of responses between treatment groups will be formally assessed using t-tests, based on an assumed approximate normal distribution for the primary outcome measure. Analyses will also be performed to identify whether there are differences between the RCT groups and the parallel patient preference groups and subsequent analysis of the merged groups if appropriate.

The results of these analyses will be used to recommend an optimal sample size, based on a formal power analysis, and design for the full RCT. In addition to the formal assessment of the primary outcome measure, analyses will also be reported for the secondary outcome measures (KOOS, Lysholm, IKDC questionnaires and EQ-5D) and complication rates reported for all groups.

**Economics analysis.** A cost-effectiveness analysis, expressed in terms of incremental costs per quality-adjusted life-year (QALY) gained, will be performed. Health-related quality of life will be estimated using the EuroQol EQ5D 5L, collected at baseline and four, eight and 12 months, and converted to a multi-attribute utility score. Results will be converted into an overall score using a published utility algorithm for the population of the United Kingdom. Unit cost data will be obtained from national databases such as the British National Formulary and Personal Social Services Research Unit

Costs of Health and Social Care. Where these are not available, the unit cost will be estimated in consultation with the UHCW finance department. Primary, community and social care service use as well as medication use will be collected using a participant questionnaire at four, eight and 12 months. A 3.5% discount rate will be used as per the National Institute for Health and Care Excellence (NICE) methods guide.

The analyses will initially take the perspective of the service provider including the costs of health and social care. Subsequent analyses will adopt a societal perspective taking into account productivity costs (time away from work) and out of pocket expenditures by the participant in relation to their treatment. A series of sensitivity analyses will be conducted to explore the effect of parameter uncertainty on the results. Cost-effectiveness modelling will also take place, based on different assumptions in regards to risk of future OA.

**Reporting plan.** This study is expected to report its findings in 2016.

**Supplementary material**

A table showing magnetic resonance imaging (MRI) protocol settings is available alongside the online version of this article at www.bjr.boneandjoint.org.uk

**References**

1. Seedholm B, Dowson D, Wright V. Functions of the menisci: a preliminary study. J Bone Joint Surg [Br] 1974;56-B:381–382.
2. Voloshin AS, Wosk J. Shock absorption of meniscectomized and painful knees: a comparative in vivo study. J Bone Joint Surg 1983;65-A:157–161.
3. Markolf KL, Mensch JS, Amstutz HC. Stiffness and laxity of the knee—the contributions of the supporting structures. A quantitative in vitro study. J Bone Joint Surg [Am] 1976;58-A:593–594.
4. Baker BE, Peckham AG, Pupparo F, Sanborn JC. Review of meniscal injury and associated sports. Am J Sports Med 1985;13:1–4.
5. Baratz ME, Fu FH, Mengato R. Meniscal tears: the effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. A preliminary report. Am J Sports Med 1986;14:270–275.
6. Roos H, Laurén M, Adalberth T, et al. Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. Arthritis Rheum 1998;41:887–893.
7. Papalia R, Del Buono A, Osti L, Denaro V, Maffulli N. Meniscectomy as a risk factor for knee osteoarthritis: a systematic review. Br Med Bull 2011;99:98–106.
8. Elattar M, Dohllander A, Verdonk R, Almqvist FK, Verdonk P. Twenty-six years of meniscal allograft transplantation: is it still experimental? A meta-analysis of 44 trials. Knee Surg Sports Traumatol Arthrosc 2011;19:147–157.
9. Bae KT, Shim H, Tao C, et al. Intra- and inter-observer reproducibility of volume measurement of knee cartilage segmented from the DAI MR image set using a novel semi-automated segmentation method. Osteoarthritis Cartilage 2009;17:1588–1597.
10. Williams TG, Holmes AP, Bowes M, et al. Measurement and visualisation of focal cartilage thickness change by MRI in a study of knee osteoarthritis using a novel image analysis tool. Br J Radiol 2010;83:940–946.
11. Varner RE, Ireland CC, Summitt RL Jr, et al. Medicine or Surgery (Ms): a randomized clinical trial comparing hysterectomy and medical treatment in premenopausal women with abnormal uterine bleeding. Control Clin Trials 2004;25:104–118.
12. Cook JA, Ramsay CR, Norrie J. Recruitment to publicly funded trials—are surgical trials really different? Contemp Clin Trials 2008;29:631–634.
13. Kerry S, Hilton S, Dunders D, Rink E, Oakeshott P. Radiography for low back pain: a randomised controlled trial and observational study in primary care. Br J Gen Pract 2002;52:469–474.
14. Rosso F, Bisicchia S, Bonasia DE, Amendola A. Meniscal Allograft Transplantation: A Systematic Review. Am J Sports Med 2015;43:998-1007.
15. Bowes MA, Vincent GR, Wolstenholme CB, Conaghan PG. A novel method for bone area measurement provides new insights into osteoarthritis and its progression. Ann Rheum Dis 2013;74:519–525.
16. Cootes TF, Edwards GJ, Taylor CJ. Active Appearance Models. IEEE Trans Pattern Anal Mach Intell 2001;23:681–685.
17. Eckstein F, Cicuttini F, Raynauld JP, Waterton JC, Peterfy C. Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): morphological assessment. Osteoarthritis Cartilage 2006;14(Suppl A):A46–A75.
18. Cicuttini F, Wluka A, Wang Y, Stuckey S. The determinants of change in patella cartilage volume in osteoarthritic knees. J Rheumatol 2002;29:2615–2619.

19. Wluka AE, Wolfe R, Stuckey S, Cicuttini FM. How does tibial cartilage volume relate to symptoms in subjects with knee osteoarthritis? Ann Rheum Dis 2004;63:264–268.

20. Lindsey CT, Narasimhan A, Adolfo JM, et al. Magnetic resonance evaluation of the interrelationship between articular cartilage and trabecular bone of the osteoarthritic knee. Osteoarthritis Cartilage 2004;12:86–96.

21. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS), from joint injury to osteoarthritis. Health Qual Life Outcomes 2003;1:64.

22. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med 1982;10:150–154.

23. Higgins LD, Taylor MK, Park D, et al. Reliability and validity of the International Knee Documentation Committee (IKDC) Subjective Knee Form. Jt Bone Spine 2007;74:594–599.

24. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

25. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095–1108.

26. No authors listed. British National Formulary. http://www.bnf.org (date last accessed 13 May 2015).

27. No authors listed. Personal Social Services Research Unit. http://www.pssru.ac.uk/ (date last accessed 13 May 2015).

28. No authors listed. National Institute for Health and Care Excellence. https://www.nice.org.uk/ (date last accessed 01 May 2015).

Funding statement:
This study has been supported by Arthritis Research UK as part of a Clinical Research Fellowship award (award number 20149).

The University of Warwick holds grants from the National Institute for Health Research and Musculoskeletal Charities for research into musculoskeletal trauma, for which M.L. Costa is an investigator - this funding is not related to this article.

C. Hutchinson reports a grant for ultrasound research from General Electric which is held by the University of Warwick and is not related to this article.

Author contributions:
N. A. Smith: Design of trial, Writing the paper
J. Achten: Writing and editing the paper
N. Parsons: Statistical input of trial design, Writing the paper
D. Wright: Comparator (physio) development, Writing the protocol for the physiotherapy, Editing the paper
B. Parkinson: Intervention input, Editing the paper
P. Thompson: Surgeon performing operations, Trial design, Editing the paper
C. E. Hutchinson: Trial design input (radiography), Development of MRI protocols, Writing the paper
T. Spalding: Senior surgeon performing operations in the trial, Trial design, Editing the paper
M.L. Costa: Data analysis, Writing the paper

ICMJE Conflict of Interest:
None declared

© Smith et al. This is an open-access article distributed under the terms of the Creative Commons Attribution license, which permits copying and redistributing the material in any medium or format, remaking, transforming and building upon the material for any purpose, even commercially, provided the original author and source are credited, and changes made are indicated. This may be done in a reasonable manner, but not in any way that suggests the licensor endorses you or your use.