RADIATE – Radial Dysplasia Assessment, Treatment and Aetiology: Protocol for the development of a core outcome set using a Delphi survey

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SUBJECT AREAS
General Medicine
Abstract

Background

Radial dysplasia (RD) is a disfiguring, potentially disabling congenital upper limb anomaly. Multiple surgical techniques are in current use, with little agreement on the optimal treatment approach. At present, no core outcome set exists specifically for radial dysplasia, and the literature is dominated by retrospective case series. A recent systematic review by this group demonstrated significant heterogeneity in both which outcomes are measured, and how they are measured.

Methods

The RADIATE study will conduct a three-round online Delphi process, involving adult radial dysplasia patients, the parents of children with radial dysplasia, hand surgeons and hand therapists. The initial list of outcomes is drawn from our recent systematic review and will be supplemented by suggestions from the stakeholder groups. Following the Delphi process, outcomes which meet the ‘consensus in’ definition will be ratified at a final consensus meeting, and a method of outcome measurement agreed for each. Where appropriate, this will overlap with the outcome measures specified in the forthcoming ICHOM congenital upper limb anomalies standard set.

Discussion

The Radial Dysplasia Assessment, Treatment and Aetiology (RADIATE) study aims to address the uncertainty in the treatment of radial dysplasia, and to begin to answer the question “what is the most appropriate treatment for children with radial dysplasia?” by establishing a core outcome set.

Trial registration

COMET initiative study 902, registered May 2016 http://www.comet-initiative.org/studies/details/902
Background

Radial dysplasia (RD) is a disfiguring, potentially disabling congenital upper limb anomaly, affecting approximately 1:8,000 births[1-3]. It is characterised by variable absence or hypoplasia of the pre-axial upper limb skeleton (radius, thumb) and soft tissues[4]. Affected children have a phenotype ranging from isolated thumb hypoplasia to complete absence of the thumb and radius, with severe ulnar bowing, elbow stiffness and humeral hypoplasia. Children may be unilaterally or bilaterally affected. Known causes include spontaneous mutations, teratogenic drugs and syndromes such as Holt-Oram, VACTERL or Fanconi anaemia, although approximately 50% of cases are of unknown aetiology. Children without associated major comorbidities can expect a normal lifespan.

Globally, several treatment techniques are in common use at specialist centres, including centralisation [5] or radialisation [6] of the ulna, either with or without prior soft-tissue distraction [7], or alternately microvascular transfer of a toe joint to act as a radial buttress to the wrist [8]. The surgical treatment of the soft tissues is highly variable. A recent systematic review by our group found patients suffer poor forearm growth and some degree of recurrent radial ‘wrist’ deviation, whether treated surgically or conservatively[9]. Currently, there is no core outcome set specifically for RD, although a generalised congenital upper limb anomaly standard set is due to be published soon [10]. Outcome measurement is further complicated because the limb changes during growth, necessitating follow-up to skeletal maturity before the final outcome can be assessed.

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Selection of outcomes for use in clinical studies of radial dysplasia
Clinical studies, whether interventional or observational, should have prospectively defined primary and secondary outcomes that answer the question(s) posed by the hypothesis. However, for existing studies of RD, the outcomes measured are numerous and highly variable between studies. The techniques for measuring many outcomes are also poorly defined, making it difficult to compare studies, or synthesise their results in a meta-analysis. It is also unclear how relevant, if at all, these outcomes are to patients themselves.

Outcome reporting bias

Another problem, especially in the surgical literature, is outcome reporting bias [11], where a large number of outcomes are measured but only those which show ‘interesting’ or ‘positive’ results are reported. This presents a biased view of the results of a trial, and by increasing the number of tests run, increases the risk of results arising by chance erroneously being labelled significant.

Core outcome sets

The development of core outcome sets (COS) is a relatively recent attempt to overcome these problems. These prospectively defined groups of outcomes represent the minimum dataset that trials in a given area should report. For paediatric conditions, they are ideally developed with patient and family involvement. By prospectively specifying the outcomes, and how they are measured, they prevent ‘cherry-picking’ of positive results, and standardise studies, allowing comparison and synthesis of their results. When developed with patients and their families, they also provide reassurance that the outcomes are relevant to patients.

Aims and Objectives

Aim

The aim of this study is to develop an initial COS suitable for assessing treatment
outcomes after any form of active or conservative treatment in patients with RD. These outcomes should apply regardless of the treatment setting.

Objectives

The specific study objectives are to list all outcomes previously reported in studies of the treatment of RD, identified through a systematic review of the literature; to prioritise outcomes from the perspective of patients, parents and clinicians; to compare patient/parent important and clinician important outcomes; and to integrate these outcomes into a combined COS.

Methods

Systematic review

We have recently published a systematic review of the long term outcomes of both surgical and conservative treatment for radial dysplasia[9]. This was prospectively registered with the PROSPERO database (CRD42016036665) and conducted using the Cochrane highly sensitive search strategy. From the studies identified, we have extracted a list of outcomes measured for radial dysplasia, which will form the starting point for our Delphi process.

Identification of outcomes of importance to patients, parents and clinicians

Overview

To achieve consensus on a COS for RD within and between groups, we propose to use an online Delphi process, adapted and simplified from the protocol laid out by Harman et al [12]. This will include four groups of participants;

- RD patients aged over 16
- Parents of RD patients aged under 16
- Hand therapists who treat RD patients
- Hand surgeons who treat RD patients
These groups were chosen to reflect patient and family perspectives equally with surgical and therapist perspectives. We aim to make the groups of similar size. Patient and parent groups will be drawn from across the UK, and clinician groups drawn from specialist centres internationally. The study will be managed from Great Ormond St Hospital in London, and participants will be recruited via email by the central research team, following identification by participating specialist centres worldwide. The Delphi process will be administered using the secure DelphiManager software at the University of Liverpool. The study process is summarised in figure 1.

Identification of potential outcomes

Our initial outcome list has been generated from the outcomes found in our systematic review. Composite outcome scores have been split into their component parts, where possible. The outcome list will be presented in alphabetical order.

Participants

We aim to recruit to the patient and parent groups via specialist centres across the UK, and to therapist and surgeon groups from global specialist centres. All participants will be required to be proficient with spoken and written English, and to have access to a computer and internet connection.

Delphi Process

Round 1 – initial ranking and finalising outcomes considered
Participant identification centres have been identified by the review authors. Potential participants will be identified by each centre locally, then invited to participate in the Delphi process by the central research team at Great Ormond St. Those who agree will be presented with an online survey, listing each identified outcome alphabetically, and providing space for other outcomes to be listed. They will be asked to rank each outcome 1-9, where 1-3 is ‘not important’, 4-6 is ‘important but not critical’ and 7-9 is ‘critical’. The online survey will allow the review author (GM), who will not himself participate, to identify who has completed the survey. Participants will be given three weeks to complete the survey, with a reminder email being sent after one and two weeks.

Analysis of round 1

Newly suggested outcomes will be reviewed by two review authors (GM and BS) to ensure they are genuinely novel, and tabulated accordingly. Results will be analysed by participant group, noting the number participating and the distribution of scores per outcome.

Individual participation in round two will be contingent upon completing the survey in round one.

Round 2 – developing consensus within each group

Participants will again be contacted by email with a link to the online survey. For each previously scored outcome, they will be presented with a summary of the responses for each group and a reminder of their previous score. They will then be asked to re-score each outcome, again from 1-9, and then to score any newly suggested outcomes identified in
round one. Participants will be given three weeks to complete the round two survey, with a reminder email being sent after one and two weeks.

Analysis of round 2

Results will be analysed both by participant group and in overall summary, noting the number participating and the distribution of scores per outcome. Individual participation in round three will again be contingent upon completing the survey in round two.

Round 3 – developing consensus between groups

Participants will again be contacted by email with a link to the online survey. For each outcome they will be presented with a summary of the responses for each group and a reminder of their round 2 score. They will then be asked to re-score each outcome, again from 1-9. Participants will be given three weeks to complete the round three survey, with a reminder email being sent after one and two weeks.

Analysis of round 3

Results will be analysed both by participant group and in overall summary, noting the number participating and the distribution of scores per outcome. Outcomes will be classified as consensus in, consensus out or no consensus using the criteria in table 1. The distribution of scores and consensus result for each outcome will be displayed by group and overall and used to structure the final consensus meeting.
Consensus meeting

A final consensus will be reached during a consensus meeting, which may involve a mixture of face to face and teleconference participation. All participants in the Delphi survey will be invited. All participants will receive the results of round three in advance, presented by group and overall. All participants will also receive a suggestion for how each outcome should be measured, which will be discussed and agreed during the consensus meeting. Where appropriate, we will aim to measure outcomes which overlap with the ICHOM standard set for congenital upper limb anomalies in the same way. The final COS will be published in a peer-reviewed journal.

Definition of consensus

We will use the definition of consensus from Harman et al [12], summarised in table 1. This will be applied to the combined group scores from round 3.

Sample size

As there is no standard model for the sample size required for a Delphi process, we will aim for between 10 - 15 participants per group, with the patient and parent groups covering patients with a variety of disease severity and age.

Discussion

There is currently no core outcome set specifically for radial dysplasia. This study seeks to develop one, with the involvement of a wide range of participants, to ensure maximal acceptability to both patients and clinicians. We also aim to overlap, where appropriate, with the wider ICHOM congenital upper limb anomalies standard set, so that patients and clinicians are not unduly burdened by outcome measurement. We hope that this outcome
set will make the interpretation, comparison and synthesis of future studies easier.

Study Status
The study protocol is version 1.0 (18 July 2018). Recruitment is due to commence in late October 2018, and to complete by November 2018. The study is expected to take 3 months once fully recruited to.

Abbreviations
BSSH British Society for Surgery of the Hand
COS Core Outcome Set
ICHOM International Consortium for Health Outcomes Measurement
PROSPERO International Prospective Register of Systematic Reviews
RADIATE Radial Dysplasia: Assessment, Treatment and Aetiology
RD Radial Dysplasia
VACTERL Vertebral, Anal, Cardiac, Tracheo-Esophageal, Renal & Limb anomalies

Declarations
Ethics approval and consent to participate
This study will be conducted in accordance with the Declaration of Helsinki. Implied informed consent will be sought from all participants prior to entry into the study. Ethical approval was granted by the London Queen Square Research Ethics Committee on 12 September 2018, REC reference 18/LO/1561.

Consent for publication
Not applicable (no individual participant data within this manuscript)

Availability of data and material
The datasets produced, used and analysed during the current study will be available in anonymised form at individual participant level from the corresponding author on reasonable request, after publication of the final study results.

Competing interests
The authors declare that they have no competing interests

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Authors’ contributions

GM conceived the study and wrote the manuscript. GM, ML, GS and BS secured ethical approval for the study, contributed to the study design, and read and approved the final manuscript.

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Authors’ information

GM is a plastic surgery registrar, a PhD student in ML’s lab at King’s College London, and the BSSH hand surgery research fellow at Great Ormond St Hospital, London.

ML is Professor of Regenerative Biology at the Randall Centre, King’s College London

GS and BS are Consultant Congenital Hand Surgeons at Great Ormond St Hospital, London.

| Table | Consensus classification | Description                                      | Definition                                      |
|-------|--------------------------|--------------------------------------------------|------------------------------------------------|
|       | Consensus in             | Consensus that outcome should be included in the core outcome set | 70% or more participants scoring 7-9, and <15% participants scoring 1-3 |
|       | Consensus out            | Consensus that outcome should not be included in the core outcome set | 70% or more participants scoring 1-3, and <15% participants scoring 7-9 |
|       | No consensus             | Uncertainty about the importance of the outcome | Any other outcome |
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Figures

![Figure 1](image)

**Figure 1**

SPIRIT figure; schedule of enrolment, interventions, and assessments.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.
