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The challenge of trial design in paediatric rheumatology

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I thank Dr Jay Mehta from the Children's Hospital of Philadelphia, Pennsylvania, USA and steering committee member of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) for his clear and helpful comments on my article (Optimizing treatment in paediatric rheumatology — lessons from oncology. *Nat. Rev. Rheumatol.* **11**, 493–499; 2015)[1], which raise important issues (Moving towards optimal therapy in paediatric rheumatology. *Nat. Rev. Rheumatol.* http://dx.doi.org/10.1038/nrrheum.2016.21)[2]. We both agree on the need to recruit all children with rheumatic disease into registries — or, even better, into treatment-optimizing studies or clinical trials. For children with cancer, this strategy has led to one of the biggest success stories in modern medicine[3]. The CARRA registry has recruited more than 9,000 patients at 62 sites and is successfully conducting collaborative research in paediatric rheumatology in North America (predominantly in the USA), Israel and Lebanon[4,5]. CARRA, funded by independent institutions and pharmaceutical companies, has formulated so-called CTPs (consensus treatment plans) for children with rheumatic diseases. In response to Dr Mehta, I would like to suggest improvement in four points regarding CARRA CTPs.

First, children with rheumatic diseases benefit from an interdisciplinary management approach, and disciplines other than paediatric rheumatology (for instance, orthopaedic and paediatric surgery, internal medicine or dermatology) need to be more heavily involved in the selection of experts and approval of CTPs. Second, the fact that a selected subset of participating physicians documents the use of a drug in a survey does not mean this treatment is effective or that it needs general recommendation; the influence of surveys on consensus-based recommendations has to be limited, as the results of these surveys are at risk of reflecting drug marketing more than solid scientific evidence. Third, and most importantly, consensus meetings only make sense if preceded by a thorough, systematic and critical literature analysis, including grading and prioritizing data from adequately designed controlled clinical trials. This analysis needs approval by the consensus participants and detailed publication together with the CTPs. As a striking example, the CARRA CTP on polyarticular juvenile idiopathic arthritis (pJIA) suggests "early combination" or "biological-only" plans that recommend the use of biologic DMARDs (bDMARD) as initial treatment[4], despite the absence of solid evidence from adequately designed controlled clinical trials for their efficacy as initial therapy in these patients. The CARRA pJIA CTP cites the trial of early aggressive therapy in pJIA (TREAT), which has an unacceptable design: children in the study arm receive etanercept as a bDMARD with methotrexate and considerable doses of steroids — the most effective short-term drug in the treatment of JIA — whereas children in the methotrexate comparator arm do not receive any steroids. Not surprisingly, efficacy in the bDMARD arm is superior[6]. All other studies of bDMARDs in pJIA had the flawed and misleading withdrawal design, as discussed in my Perspectives article[1]. By contrast, results from the Canadian cohort 'research in arthritis in Canadian children emphasizing outcomes study' (ReACCh-Out), which included 1,104 children with JIA (including 235 patients with rheumatoid-factor-negative polyarthritis), showed inactive disease after 2 years in most patients without use of bDMARDS as initial treatment[7]. Fourth, the precise role of the pharmaceutical industry, and the extent of its funding of CARRA and their CTPs, should be clarified and made more transparent in all CARRA publications.

In my view, the approach of CARRA CTPs is highly desirable and a very important step towards prospective data collection and treatment standardization. However, an interdisciplinary and transparent approach, as well as a clear commitment to evidence-based medicine, is vital. An array of exciting new drugs is on the horizon, both in paediatric rheumatology and oncology, which will need the scientific community and regulatory bodies to push for independent, investigator-initiated clinical research on a high level. Flawed trial design (inclusion of responders only in withdrawal designs, or inadequate control groups as in the TREAT study) may help pharmaceutical companies get licensing for their drugs, but might result in data sets of questionable clinical importance and put children at unnecessary risk.

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1. Niehues, T. Optimizing treatment in paediatric rheumatology — lessons from oncology. *Nat. Rev. Rheumatol.* **11**, 493–499 (2015).
2. Mehta, J. Moving towards optimal therapy in paediatric rheumatology. *Nat. Rev. Rheumatol.* (2016).
3. Cole, C. H. Lessons from 50 years of curing childhood leukaemia. *J. Paediatr. Child Health* **51**, 78–81 (2015).
4. Ringold, S. *et al.* Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for new-onset polyarticular juvenile idiopathic arthritis. *Arthritis Care Res. (Hoboken)* **66**, 1063–1072 (2014).
5. CARRA. Childhood Arthritis and Rheumatology Research Alliance. *CARRA* [online], https://www.carragroup.org (2016).
6. Wallace, C. A. *et al.* Extension study of participants from the trial of early aggressive therapy in juvenile idiopathic arthritis. *J. Rheumatol.* **41**, 2459–2465 (2014).
7. Guzman, J. *et al.* The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. *Ann. Rheum. Dis.* **74**, 1854–1860 (2015).

Competing interests statement
The author declares no competing interests.