Use of clinical, surrogate, and intermediate endpoints in randomized controlled Fontan trials

ten Dam K. (1,2), Germund I. (3), Haustein M. (3), Khalil M. (4), Koopman L.P. (1,2), Apitz C. (5),
Duijnhouwer A.L. (6), Huntgeburth M. (7), Brockmeier K. (3), Helbing W.A. (1,2), Hannes T. (3),
Herberg U. (8), Sreeram N. (3), Tanke R.B. (1,2), Kerst G. (9), Udink ten Cate F.E.A. (1,2)
[for the Fontan Care Network].
Amalia Children’s Hospital, Radboud University Medical Center, Nijmegen, the Netherlands (1);
Sophia Children’s Hospital, Erasmus Medical Center, Rotterdam, the Netherlands (2); Heart Center
Cologne, University Hospital Cologne, Cologne, Germany (3); Pediatric Heart Center, Justus-Liebig
University, Giessen, Germany (4); University Children’s Hospital Ulm, Ulm, Germany (5); Department
of Cardiology, Radboud University Medical Center, Nijmegen, Netherlands (6); Clinic III for Internal
Medicine, Department of Cardiology, Heart Center, University Hospital Cologne, Cologne, Germany
(7); University of Bonn, Bonn, Germany (8); University Hospital RWTH Aachen, Aachen, Germany (9)

Objectives. Randomized controlled trials (RCT) are pivotal for directing evidence-based clinical care.
Selection of meaningful endpoints is an essential part of the study design of an RCT. However, no
study has systematically examined endpoint selection in Fontan RCTs. In the present study we sought
to examine trends in endpoint selection in contemporary Fontan RCTs.

Methods. A search of the PubMed database was conducted using the keywords ‘Fontan circulation’,
Fontan’ AND ‘randomized controlled trial’ OR ‘randomized prospective study’ to identify all Fontan
RCTs published from 2002 to 2017. The following data were extracted from each identified trial: (1)
journal, (2) year of publication, (3) study design, (4) intervention, (5) number of patients, (6) number
of participating sites and countries, (7) endpoints (primary and secondary), (8) whether the trial met its
intended endpoints, and (9) funding sources.Endpoints were categorized as clinical, intermediate or
surrogate.

Results. Twenty-two RCT’s were found eligible for inclusion. A total of 979 Fontan patients were
included in the final analysis. Forty-six primary endpoints were identified. A median of 1 primary
endpoint (range 1 - 9) was used per RCT. Eight (17.4%) endpoints were clinical. The majority of these
endpoints were categorized as intermediate (n = 25, 54.3%). Change in peak VO2 was most
commonly used (n=8). A total of 100 secondary endpoints were identified, mainly categorized as
intermediate (n = 47, 47.0%). Change in heart rate (n = 4) was the most frequently used secondary
endpoint. Only nine trials (40.9%) met their intended endpoints. Of the 7 RCT’s using clinical
endpoints, none were able to reject the null hypothesis. Surrogate and intermediate endpoints were
frequently combined in the RCTs (n = 15, 68.2%).

Conclusions. This study is the first to demonstrate the heterogeneity and the frequent use of
intermediate and surrogate endpoints in contemporary Fontan RCTs. There is a great need to develop
validated and standardized endpoints in Fontan research.