



This is a repository copy of *Repeatability and sensitivity to change of non-invasive end points in PAH: the RESPIRE study*.

White Rose Research Online URL for this paper:
<https://eprints.whiterose.ac.uk/182837/>

Version: Published Version

Article:

Swift, A.J. orcid.org/0000-0002-8772-409X, Wilson, F., Cogliano, M. et al. (20 more authors) (2021) Repeatability and sensitivity to change of non-invasive end points in PAH: the RESPIRE study. *Thorax*, 76 (10). pp. 1032-1035. ISSN 0040-6376

<https://doi.org/10.1136/thoraxjnl-2020-216078>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:
<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>



OPEN ACCESS

Repeatability and sensitivity to change of non-invasive end points in PAH: the RESPIRE study

Andrew J Swift,¹ Frederick Wilson,² Marcella Cogliano,¹ Lindsay Kendall,² Faisal Alandejani,¹ Samer Alabed,¹ Paul Hughes,¹ Yousef Shahin,¹ Laura Saunders,¹ Charlotte Oram,¹ David Capener,¹ Alex Rothman,¹ Pankaj Garg,¹ Christopher Johns ,¹ Matthew Austin,¹ Alistair Macdonald,¹ Jo Pickworth,¹ Peter Hickey,¹ Robin Condliffe,³ Anthony Cahn,^{2,4} Allan Lawrie,¹ Jim M Wild,¹ David G Kiely^{1,3}

► Additional material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2020-216078>).

¹Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield, Sheffield, UK

²Research and Development, GlaxoSmithKline, Stevenage, UK

³Sheffield Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, UK

⁴Department of Respiratory Medicine, Bedford Hospital, Bedford, UK

Correspondence to

Dr Andrew J Swift, Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield, Sheffield S10 2JF, UK; a.j.swift@sheffield.ac.uk

Received 24 August 2020

Revised 20 January 2021

Accepted 8 February 2021

Published Online First

25 February 2021

Abstract End points that are repeatable and sensitive to change are important in pulmonary arterial hypertension (PAH) for clinical practice and trials of new therapies. In 42 patients with PAH, test–retest repeatability was assessed using the intraclass correlation coefficient and treatment effect size using Cohen’s d statistic. Intraclass correlation coefficients demonstrated excellent repeatability for MRI, 6 min walk test and log to base 10 N-terminal pro-brain natriuretic peptide (\log_{10} NT-proBNP). The treatment effect size for MRI-derived right ventricular ejection fraction was large (Cohen’s d 0.81), whereas the effect size for the 6 min walk test (Cohen’s d 0.22) and \log_{10} NT-proBNP (Cohen’s d 0.20) were fair. This study supports further evaluation of MRI as a non-invasive end point for clinical assessment and PAH therapy trials.

Trial registration number NCT03841344.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is progressive, leading to right ventricular (RV) failure and death.¹ Accurate measurement of RV function is important for assessment of disease severity and prognosis.^{2–4} Despite new therapies and improvements in survival,⁵ PAH remains a life-shortening condition. MRI is the gold standard for RV assessment,⁶ has prognostic value² and predicts clinical worsening⁷ in PAH. A trial end point that is highly repeatable, is sensitive to treatment and predicts outcomes would be highly desirable.^{8,9} MRI has been proposed as a trial end point in PAH,^{8,9} however, there is limited data on repeatability and treatment effect size.

METHODS

Patients

Patients with PAH who were treatment-naïve commencing therapy, prevalent undergoing escalation of therapy and clinically stable requiring no escalation of therapy, were recruited. See online supplemental file S1.

Study investigations

Investigations performed at visit 1 included N-terminal pro-brain natriuretic peptide (NT-ProBNP), 6 min walk test (6MWT) and MRI. Follow-up visits 2 and 3 occurred approximately 6 months after study visit 1. Visits 2 and 3 occurred within 24 hours of each other (online supplemental figure S2).

MRI acquisition and analysis

All MRI examinations were performed on either a 1.5 T GE HDx (GE Healthcare, Milwaukee, USA) whole body scanner using an 8-channel cardiac coil or a 3 T Philips Ingenia (Best, The Netherlands) whole body scanner using a 32-channel dStream torso coil (online supplemental file S1). Analysis of MRI was undertaken blinded to the patient’s data. RV parameters and pulmonary arterial flow were analysed on Qmass MEDIS suite (V3.0.18.0, Medical Imaging Systems, The Netherlands) on short axis and phase contrast images, respectively. Regions of interest were drawn on the pulmonary artery and left atrium of the dynamic contrast-enhanced perfusion images to calculate first pass pulmonary transit time and full width at half maximum using in-house software (see online supplemental figure S3).

Six min walk test and NT-ProBNP

The 6MWT was performed by a respiratory physiologist. NT-ProBNP analysis was performed on patient plasma samples using the Luminex 100/200 multiplex analyser using the cardiovascular marker kit (HCVD-1MAG-67K Millipore) at the end of the study.

Statistical analysis

Repeatability was determined by the intraclass correlation coefficient (ICC) using a two-way mixed absolute agreement model with the average measure recorded. An ICC of ≥ 0.75 was considered excellent, 0.60–0.74 good, 0.40–0.59 fair and < 0.40 poor. Mean difference and 95% CIs were presented where appropriate. Cohen’s d (calculated with the averaged SD, d_{av}) was used to assess the standardised treatment effect size between visit 1 and visit 2.¹⁰ A Cohen’s d value of < 0.20 was considered no change, 0.20–0.49 was considered fair change, 0.50–0.79 was considered a medium change and ≥ 0.80 was considered a large change. All analysis was performed on SPSS V.22 and GraphPad Prism V.16.

RESULTS

Patients

Of 42 patients who completed the study, 16 were incident and treatment-naïve and initiated PAH therapy, 12 were prevalent and underwent an escalation of therapy and 14 were stable on therapy with no change in treatment occurring between the study visits. (online supplemental table S5).



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY. Published by BMJ.

To cite: Swift AJ, Wilson F, Cogliano M, *et al.* *Thorax* 2021;**76**:1032–1035.



Table 1 Repeatability in all patients with PAH (ICC), and treatment effect size for patients with PAH initiating or escalating PAH therapy

| | All PAH | | Patients with PAH initiating or escalating therapy | | | | | | | | | | |
|--|---------|-------|--|---------|--------|---------|--------|--------------------------|--------|-------|--------|-------|-----------|
| | N | ICC | N | Visit 1 | | Visit 2 | | Change (Visit 1–visit 2) | | | 95% CI | | Cohen's d |
| | | | | Mean | SD | Mean | SD | Mean difference | SD | SEM | Lower | Upper | |
| Walk test | | | | | | | | | | | | | |
| 6MWT distance (m) | 39 | 0.987 | 24 | 325.63 | 156.30 | 361.50 | 166.29 | –35.88 | 79.06 | 16.14 | –69.26 | –2.49 | 0.22 |
| Blood tests | | | | | | | | | | | | | |
| Log NT-ProBNP | 32 | 0.772 | 24 | 2.76 | 0.46 | 2.67 | 0.41 | 0.09 | 0.32 | 0.07 | –0.05 | 0.22 | 0.20 |
| MRI metrics | | | | | | | | | | | | | |
| <i>SA with threshold</i> | | | | | | | | | | | | | |
| RVEDM (g) | 40 | 0.970 | 26 | 117.80 | 45.72 | 99.40 | 43.96 | 18.40 | 30.90 | 6.06 | 5.92 | 30.88 | 0.41 |
| RVESM (g) | 40 | 0.980 | 26 | 106.68 | 39.73 | 94.61 | 42.08 | 12.06 | 26.79 | 5.25 | 1.24 | 22.88 | 0.29 |
| RVEDV (mL) | 40 | 0.969 | 26 | 145.71 | 39.12 | 146.03 | 55.87 | –0.32 | 29.13 | 5.71 | –12.08 | 11.45 | 0.01 |
| RVESV (mL) | 40 | 0.983 | 26 | 93.93 | 34.66 | 81.28 | 41.40 | 12.65 | 22.02 | 4.32 | 3.76 | 21.55 | 0.33 |
| RVEF (%) | 40 | 0.883 | 26 | 36.56 | 11.48 | 45.69 | 11.12 | –9.12 | 10.45 | 2.05 | –13.35 | –4.90 | 0.81 |
| RVSV (mL) | 40 | 0.864 | 26 | 51.78 | 17.30 | 64.75 | 23.92 | –12.97 | 23.27 | 4.56 | –22.37 | –3.57 | 0.62 |
| RVCO (L/min) | 40 | 0.886 | 26 | 3.95 | 1.45 | 4.48 | 1.55 | –0.53 | 1.54 | 0.30 | –1.15 | 0.09 | 0.35 |
| Systolic septal angle (°) | 40 | 0.852 | 27 | 163.33 | 16.45 | 156.81 | 14.00 | 6.52 | 11.28 | 2.17 | 2.06 | 10.98 | 0.43 |
| Diastolic septal angle (°) | 40 | 0.897 | 27 | 153.11 | 14.73 | 145.48 | 10.44 | 7.63 | 10.15 | 1.95 | 3.61 | 11.65 | 0.60 |
| Q flow | | | | | | | | | | | | | |
| Net flow volume (mL) | 41 | 0.893 | 26 | 58.05 | 30.18 | 69.49 | 31.30 | –11.44 | 34.83 | 6.83 | –25.51 | 2.62 | 0.37 |
| Forward flow volume (mL) | 41 | 0.860 | 26 | 60.37 | 27.58 | 72.33 | 29.15 | –11.96 | 31.97 | 6.27 | –24.88 | 0.95 | 0.42 |
| Backward flow volume (mL) | 41 | 0.817 | 26 | 2.32 | 6.76 | 2.84 | 5.74 | –0.52 | 5.85 | 1.15 | –2.88 | 1.85 | 0.08 |
| Regurgitant fraction (%) | 41 | 0.731 | 26 | 6.28 | 19.58 | 5.42 | 11.52 | 0.87 | 18.77 | 3.68 | –6.71 | 8.45 | 0.05 |
| Average flow velocity (cm/s) | 41 | 0.909 | 26 | 7.31 | 3.60 | 8.25 | 3.69 | –0.94 | 3.69 | 0.72 | –2.43 | 0.55 | 0.26 |
| Peak flow velocity (cm/s) | 41 | 0.582 | 26 | 52.97 | 16.37 | 67.68 | 22.71 | –14.71 | 19.35 | 3.79 | –22.53 | –6.90 | 0.74 |
| Diastolic vessel area (mm ²) | 41 | 0.933 | 26 | 981.10 | 257.92 | 961.84 | 242.96 | 19.26 | 104.52 | 20.5 | –22.96 | 61.48 | 0.08 |
| Systolic vessel area (mm ²) | 41 | 0.953 | 26 | 1077.57 | 279.96 | 1083.62 | 266.78 | –6.05 | 101.08 | 19.82 | –46.88 | 34.77 | 0.02 |
| Pulmonary arterial pulsatility (%) | 41 | 0.776 | 26 | 9.96 | 4.87 | 13.00 | 5.12 | –3.04 | 3.62 | 0.71 | –4.50 | –1.58 | 0.61 |
| DCE imaging | | | | | | | | | | | | | |
| Pulmonary transit time (s) | 36 | 0.728 | 21 | 6.76 | 1.81 | 6.12 | 1.88 | 0.64 | 1.60 | 0.35 | –0.09 | 1.37 | 0.35 |
| FWHM (s) | 32 | 0.906 | 18 | 7.89 | 3.14 | 6.20 | 2.40 | 1.68 | 2.19 | 0.52 | 0.60 | 2.77 | 0.60 |

Data are shown for all patients with PAH initiating or escalating PAH therapy.

DCE, dynamic contrast-enhanced imaging; FWHM, full width at half maximum; ICC, intraclass correlation coefficient; Log₁₀NT-ProBNP, log to base 10 N-terminal pro-brain natriuretic peptide; 6MWT, six min walk test; PAH, pulmonary arterial hypertension; RVCO, right ventricular cardiac output; RVEDM, right ventricle end-diastolic mass; RVEDV, right ventricle end-systolic volume; RVEF, right ventricle end-systolic volume; RVESM, right ventricle end-systolic mass; RVSV, right ventricle stroke volume; SA, short axis.

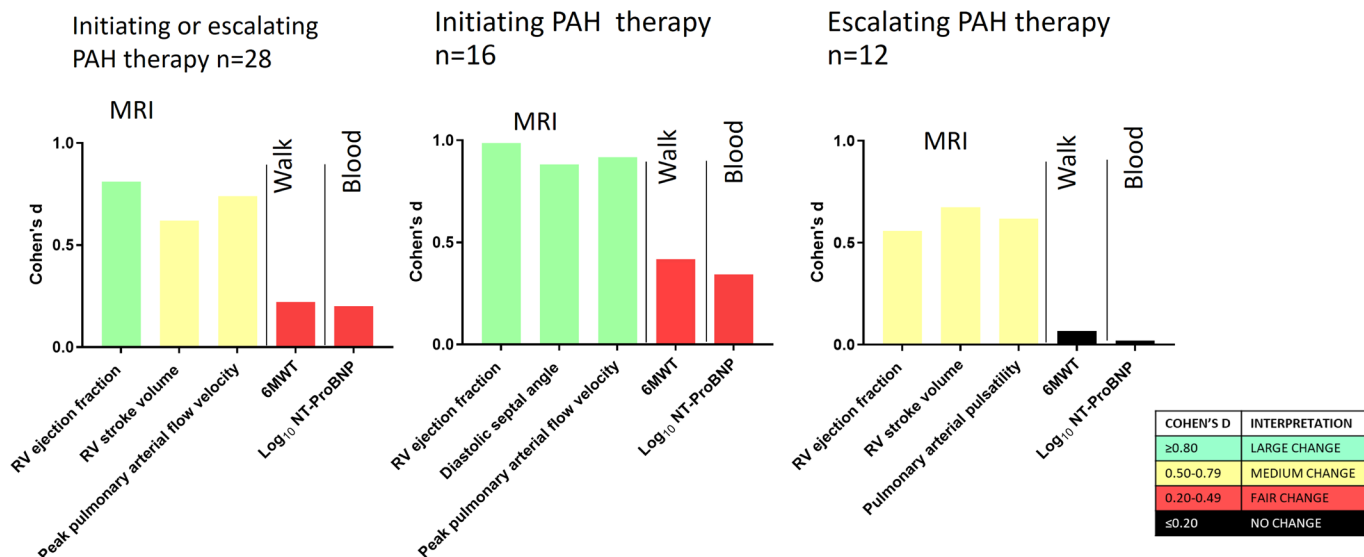


Figure 1 Comparison of treatment effect size using Cohen's d results in patients initiating and/or escalating pulmonary arterial hypertension (PAH) therapy. 6MWT, 6 min walk test; Log₁₀NT-ProBNP, log to base 10 N-terminal pro-brain natriuretic peptide; RV, right ventricular.

Test–test repeatability (visits 2 and 3)

In patients with PAH, test–test repeatability was assessed between visits 2 and 3; 6MWT (ICC 0.987) and log₁₀NT-ProBNP (ICC 0.772) had excellent repeatability. Of cardiac MRI metrics (table 1), all showed excellent repeatability. Data for MRI pulmonary flow and perfusion transit times are shown in table 1.

Treatment effect size (visits 1 and 2)

For all patients, initiating or escalating therapy (n=28), the only measurement with a large treatment effect size was RV ejection fraction (Cohen's d 0.81). The 6MWT (Cohen's d 0.22) and NT-ProBNP (Cohen's d 0.20) demonstrated a fair treatment effect size (table 1). Figure 1 shows Cohen's d values for the

top three MRI end points, the 6MWT and NT-proBNP. Figure 2 shows ICC versus Cohen's d value for all end points. In patients initiating PAH therapy, RV ejection fraction (Cohen's d 0.99), diastolic septal angle (Cohen's d 0.88) and peak pulmonary arterial flow velocity (Cohen's d 0.92) had a large treatment effect size. In patients escalating therapy, RV ejection fraction, RV stroke volume and pulmonary arterial pulsatility had a medium effect size, whereas NT-ProBNP (Cohen's d 0.02) and 6MWT (Cohen's d 0.07) demonstrated no treatment effect (see online supplemental figure S4). The stable patient group showed either no or fair changes across all measured parameters (online supplemental table S6).

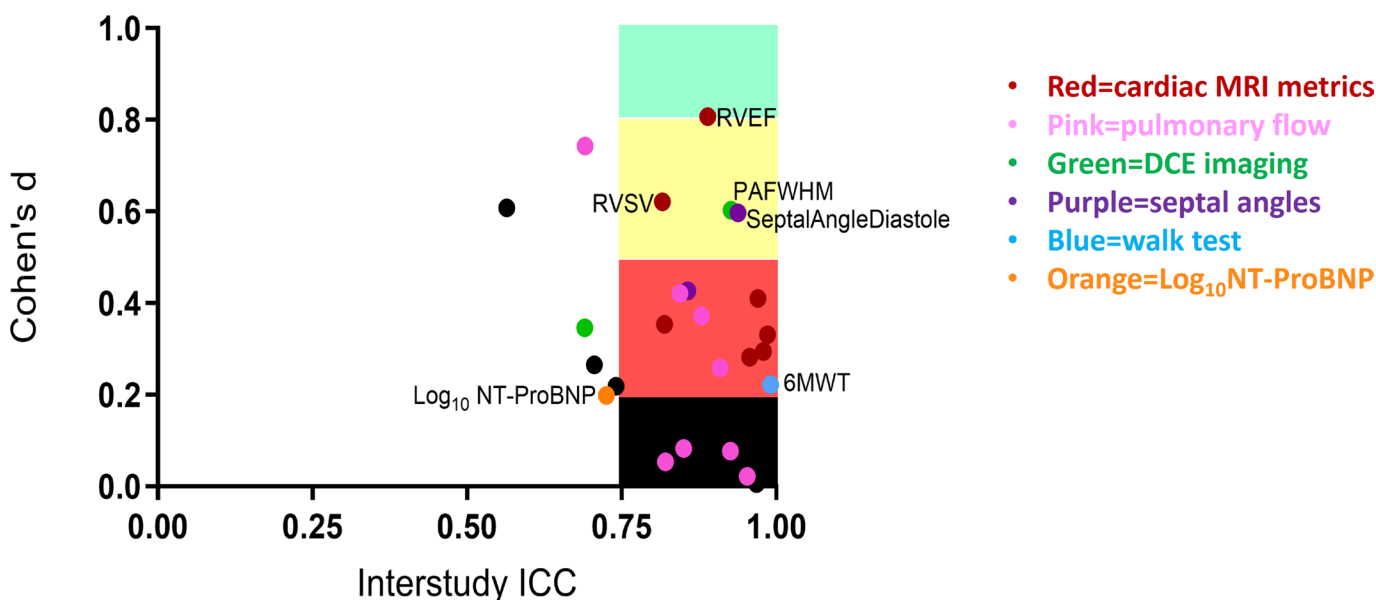


Figure 2 Cohen's d versus interstudy intraclass correlation coefficient (ICC) for study measurements. DCE, dynamic contrast-enhanced imaging; Log₁₀NT-ProBNP, log to base 10 N-terminal pro-brain natriuretic peptide; PAFWHM, pulmonary arterial full width at half maximum; RVEF, right ventricular ejection fraction; RSV, right ventricle stroke volume; 6MWT 6 min walk test. ICC >0.75=excellent repeatability. Cohen's d value of <0.20 was considered no change, 0.20–0.49 was considered a fair change, 0.50–0.79 was considered a medium change and ≥0.80 was considered a large change.

DISCUSSION

Investigations used to monitor disease severity in patients with PAH, namely 6MWT distance, NT-ProBNP level and MRI metrics, had excellent repeatability. In contrast, only MRI (RVEF) demonstrated a large treatment effect size in patients initiating or escalating therapies, whereas for the 6MWT and NT-ProBNP the treatment effect sizes were fair.

As observed in previous clinical trials¹ and highlighted at the 6th World Symposium,⁹ all metrics evaluated in patients with PAH escalating therapy had a lower treatment effect size compared with treatment-naïve patients initiating therapy. This represents a challenge when studying the effects of new therapies in PAH where the standard of care is combination treatment.¹ Importantly, MRI was still able to detect a medium treatment effect size in patients receiving background PAH therapy. Due to the large cost of conducting PAH therapy trials, strategies to reduce the size of studies and their duration using a surrogate end point that is repeatable and has a large treatment effect size would be highly desirable.⁹

This study has a number of limitations including the small sample size and the lack of comparison with invasively measured pulmonary haemodynamics. Nonetheless, we have demonstrated in this exploratory study that MRI, the gold standard for RV function assessment, detects a larger treatment effect than the 6MWT or NT-proBNP. This may reflect the ceiling effect of the 6MWT and the effect of comorbidities (including chronic kidney disease) that may influence 6MWT distance and NT-proBNP levels. MRI metrics predict clinical worsening⁷ and mortality^{2–4} fulfilling many of the criteria of a surrogate end point.⁹ Given that pulmonary haemodynamics are commonly used in early phase PAH studies,¹ a direct comparison of MRI metrics and pulmonary haemodynamics, to detect longitudinal change following PAH therapy, is now required if MRI imaging is to be considered a primary end-point for PAH therapy trials.^{8,9}

This study demonstrates the high repeatability of MRI metrics in PAH and the large treatment effect size support further evaluation of MRI as a non-invasive endpoint in PAH therapy trials.

Correction notice This article has been corrected since it was published Online First. Affiliations for FW and AC have been updated.

Acknowledgements The authors would like to thank Elizabeth Berry for her help with study logistics, data analysis and manuscript quality checks, and for taking an active role on the steering committee. The authors would like to thank Amanda Creaser-Myers, Sara Walker, Kathryn Birchall and Mercy Korley for their assistance with the patient consenting process and taking blood samples. The authors would like to thank Jennifer Rodgers for help with database management and with administrative support. The authors would like to thank Dave Capener who acquired the MRI images for several of the cases. The authors would like to thank Charlie Elliot and Athanios Charalampopoulos for aiding study recruitment. The authors would like to thank Martin Brook for his help with MRI scan management. The authors would like to thank Jim Lithgow for his assistance with research governance approvals. The authors would like to thank the late Susie Fowles who was integral to the set up of the study, set up of the steering committee and had a major role in the development of the study protocol. Finally, the authors would also like to thank Carl Burgess, the patient representative, who actively contributed to the study design and execution through participation in the steering committee and also contributed expertise and practical assistance with data management.

Contributors AJS, FW, JMW, AC, LK, DGK conceived the idea for the study. MC, MA, DGK, RC, AJS supported patient recruitment. AJS, JMW, DGK, AM, PH, LS devised the MRI protocol. AJC, CO, PH, LS analysed the MRI studies. FA, AM, CJ, PH, PG performed data quality control checks. MA performed the walk tests and FA, JP, AL performed the lab analyses. MC, LK, SA, AR, PG, AJS, YS, FS, PH, LS supported the data collation and analysis. Statistical analysis was performed by MC, SA, AJS, FA, LS, LK. All authors contributed to the drafting of the manuscript. All authors approved the final version of the manuscript.

Funding This study was funded by GlaxoSmithKline (contract number COL100041816) and Wellcome Trust (205188/Z/16/Z and 206632/Z/17/Z). PH is funded by a research grant from GlaxoSmithKline (BIDS3000032592).

Competing interests FW, LK and AC are employees and shareholders of GlaxoSmithKline. AS is the principal investigator for the collaborative research grant from GlaxoSmithKline that funded this study. AS has undertaken consultancy work for General Electric and Actelion Pharmaceuticals. RC has received fees for lecturing and participation in advisory boards, from Actelion, Bayer, GSK and MSD. DGK has received fees for lecturing and participation in advisory boards, from Actelion, Bayer, GSK and MSD and fees for participation in Steering Committees for Actelion.

Patient consent for publication Not required.

Ethics approval Ethical approval was obtained and patients provided written consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

ORCID iD

Christopher Johns <http://orcid.org/0000-0003-3724-0430>

REFERENCES

- Galiè N, Humbert M, Vachiery J-L, *et al*. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint Task force for the diagnosis and treatment of pulmonary hypertension of the European Society of cardiology (ESC) and the European respiratory Society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPCC), International Society for heart and lung transplantation (ISHLT). *Eur Heart J* 2016;37:67–119.
- Swift AJ, Capener D, Johns C, *et al*. Magnetic resonance imaging in the prognostic evaluation of patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2017;196:228–39.
- Lewis RA, Johns CS, Cogliano M, *et al*. Identification of cardiac magnetic resonance imaging thresholds for risk stratification in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2020;201:458–68.
- van de Veerdonk MC, Kind T, Marcus JT, *et al*. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol* 2011;58:2511–9.
- Hurdman J, Condliffe R, Elliot CA, *et al*. ASPIRE registry: assessing the spectrum of pulmonary hypertension identified at a referral centre. *Eur Respir J* 2012;39:945–55.
- Grothues F, Moon JC, Bellenger NG, *et al*. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *Am Heart J* 2004;147:218–23.
- Alabed S, Shahin Y, Garg P, *et al*. Cardiac-MRI predicts clinical worsening and mortality in pulmonary arterial hypertension: a systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2020. doi:10.1016/j.jcmg.2020.08.013. [Epub ahead of print: 30 Sep 2020].
- Kiely DG, Levin D, Hassoun P, *et al*. Express: statement on imaging and pulmonary hypertension from the pulmonary vascular research Institute (PVRI). *Pulm Circ* 2019;2045894019841990. doi:10.1177/2045894019841990
- Sitbon O, Gomberg-Maitland M, Granton J, *et al*. Clinical trial design and new therapies for pulmonary arterial hypertension. *Eur Respir J* 2019;53:1801908.
- Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front Psychol* 2013;4:863.