To the Editor:

The advent of antifibrotic agents [1, 2] as standard of care in idiopathic pulmonary fibrosis (IPF) requires that new non-inferiority IPF drug trials will need to identify smaller declines of forced vital capacity (FVC). Marginal annualised FVC declines (between 5.00 and 9.99%) are particularly challenging to interpret as they might reflect measurement variation or genuine clinical deterioration [3]. Following on from previous baseline-only computed tomography (CT) analyses [4], the current study examined whether changes in computer features (CALIPER) across serial CT examinations could be considered as a trial co-endpoint, particularly with regard to adjudicating marginal FVC declines, and therefore improve the sensitivity of IPF drug trials.

Previous baseline IPF analyses identified that variable initiation time, dosages, durations and types of antifibrotic medication in study participants had a profound confounding effect on mortality relationships [4]. Consequently, analyses in the current manuscript were restricted to IPF patients not receiving anti-fibrotic therapy (discovery cohort: n=71 Royal Brompton Hospital patients presenting from January 2007 to December 2014; validation cohort: n=24 St Antonius Hospital, Nieuwegein patients presenting from January 2005 to June 2014 and n=23 Mayo Clinic Rochester patients presenting from January 2009 to June 2015). All patients had two non-contrast volumetric CT scans between 5 and 30 months apart (mean CT interval: discovery cohort 1.1 years; validation cohort 1.2 years) as part of their clinical care. Baseline diffusion capacity of the lung for carbon monoxide ($D_L$CO) and FVC (baseline and longitudinal) were collected if performed within 3 months of the respective CTs. No patients were lost to follow-up.

Annualised FVC change was measured using a linear mixed effects model on all eligible timepoints to derive the best linear unbiased predictor (BLUP) as previously described using the lmer function from the R package lme4 [5]. A naïve estimate of FVC change was also examined using FVC measurements at the first and second CT timepoint. For the naïve estimate we computed annual relative change by dividing the absolute annual change by the baseline FVC value (relative). Dichotomised relative FVC declines (≥5% or ≥10%) were derived based on the naïve and BLUP estimates. Of the 27 CALIPER features examined [4], nine were measured on a whole lung level: total lung volume, normal parenchyma, vessel-related structures (CAL VRS), emphysema, honeycombing, reticular pattern and ground-glass opacity. Fibrosis extent summed reticular pattern and honeycombing. Interstitial lung disease extent additionally summed ground-glass opacification. 18 CAL VRS subdivisions were evaluated, separated according to lung zonal location: upper (UZ), middle (MZ) and lower zones (LZ), and cross-sectional area of structures in each zone: <5 mm$^{-2}$, 5–10 mm$^{-2}$, 10–15 mm$^{-2}$, 15–20 mm$^{-2}$, >20 mm$^{-2}$. Volumes for all CALIPER features were converted into a percentage using CALIPER-derived total lung volume measurements [6, 7]. Absolute change in the derived 27 CT variables was annualised by dividing by the time interval between the two measurements (in years). Cox proportional hazards models examined CALIPER and FVC change variables in separate discovery and validation cohorts. Time was measured from the second CT. An event was either death (n=90) or transplantation (n=8). Each predictor variable was tested alone while correcting for patient age (at the second CT) and gender. Model fit was evaluated using the concordance index, which assesses how well the ordering of subjects for the actual time of the event agrees with the predicted outcome. The vessel-related structures, a computer-derived CT variable, is a strong predictor of outcome in idiopathic pulmonary fibrosis and can increase power in future drug trials when used as a co-endpoint alongside forced vital capacity change. Change in the vessel-related structures, a computer-derived CT variable, is a strong predictor of outcome in idiopathic pulmonary fibrosis and can increase power in future drug trials when used as a co-endpoint alongside forced vital capacity change. Change in the vessel-related structures, a computer-derived CT variable, is a strong predictor of outcome in idiopathic pulmonary fibrosis and can increase power in future drug trials when used as a co-endpoint alongside forced vital capacity change. Change in the vessel-related structures, a computer-derived CT variable, is a strong predictor of outcome in idiopathic pulmonary fibrosis and can increase power in future drug trials when used as a co-endpoint alongside forced vital capacity change.
rather than selecting one over another. A important yet distinct surrogate measures of mortality and argues for their integration as co-endpoints. The weak correlations between FVC change and VRS change indicate that both variables represent 

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the utility of a CAL VRS threshold 

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reach the composite endpoint than a solitary endpoint of 

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different to those experiencing an FVC decline 

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patients not exposed to antifibrotic medication. Patients exhibiting a CAL VRS increase 

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in a computer-derived variable, the vessel-related structures (CAL VRS), strongly predicts mortality in IPF 

Our findings demonstrate that in independent discovery and validation populations, an absolute increase 

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79/118 (67%) patients reached a CAL VRS of 

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independently predicted mortality when evaluated against a 

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CAL VRS thresholds 

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identified. When all patients with an FVC decline more than 5% and less than 10% were subanalysed, 

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combined endpoint of an increase in a CALIPER variable and an FVC 

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decline threshold (figure 1c). When CAL VRS and UZ VRS elevation thresholds 

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0.30% independently predicted mortality when evaluated against a 

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79/118 (67%) patients reached a CAL VRS of 

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whilst 54/118 (46%) reached a 

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FVC decline threshold (p=0.0003). 89/118 (75%) patients reached either the CAL VRS threshold of 

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change or 

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FVC decline threshold (figure 1c). Use of a CAL VRS increase threshold of 

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change identified 35/118 (30%) more patients reaching an endpoint than the 

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FVC decline threshold alone. Similarly, at least 30% more patients reached an endpoint when an UZ VRS threshold was used 

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alongside a 

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FVC decline threshold (figure 1c). When CAL VRS and UZ VRS elevation thresholds 

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were examined against a 

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FVC decline threshold, additional patients reaching an endpoint were again 

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identified. When all patients with an FVC decline more than 5% and less than 10% were subanalysed, 

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CAL VRS thresholds 

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change demonstrated C-indices that were at least equivalent to a 

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FVC decline threshold (figure 1d).

Our findings demonstrate that in independent discovery and validation populations, an absolute increase 

in a computer-derived variable, the vessel-related structures (CAL VRS), strongly predicts mortality in IPF 

patients not exposed to antifibrotic medication. Patients exhibiting a CAL VRS increase 

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were different to those experiencing an FVC decline 

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Accordingly, if a composite endpoint of CAL VRS 

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increase and/or 

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FVC decline were used in a drug trial setting, 30% more patients would reach the composite endpoint than a solitary endpoint of 

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FVC decline. Our findings also suggest 

the utility of a CAL VRS threshold 

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increase as an arbitration tool for marginal FVC declines 

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between 5.0 and 9.9%).

The weak correlations between FVC change and VRS change indicate that both variables represent 

important yet distinct surrogate measures of mortality and argues for their integration as co-endpoints rather than selecting one over another. A 

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increase in VRS across a cohort appeared to be the most accurate measure of change in VRS, when considering both its prognostic effect when judged against FVC decline and its sensitivity as an endpoint. In an individual, whilst the most accurate threshold for VRS change may also be a 

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threshold, further work is necessary to establish optimal thresholds for use 

in clinical practice, as just having knowledge of the range of change of a variable does not of course provide any statement of the clinical significance of that change. For example, it was noticeable that more extreme VRS cut-offs, e.g. 0.75%, made even more of a difference in model fit and C-index than a 

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But we cannot know how often such a magnitude of VRS change would be seen in a clinical trial population. A logical next analytic step would therefore be to evaluate VRS change in a well-controlled drug trial population receiving antifibrotics at a standardised dosing regimen.

The validity of VRS change was considered according to the OMERACT filter criteria for IPF clinical trial domains [9]. Regarding truth and discrimination criteria, VRS change was considered to be more...
discriminatory than FVC change at predicting outcome, with potential for use as a continuous variable (with no loss of signal strength), or as a binary threshold alongside an FVC decline threshold to improve endpoint sensitivity. The variable therefore satisfies construct, content and criterion validity and demonstrates sensitivity to change.

The specific impact on VRS change of differing inspiratory effort, acquisition or reconstruction parameters has not been systematically investigated, and further study is indicated. However, our analysis of this measure in a heterogeneous dataset from multiple institutions suggests this is robust. CALIPER outputs are eminently interpretable and feasible to perform but real-world utility of VRS for clinical trials relies on availability of repeated CTs and the computer algorithm, and is therefore limited when compared to FVC measurements.

There were limitations to the current study. Though there were similar average CT intervals between the two study cohorts and change in CT variables were reported as annualised change, the CTs time intervals were not standardised in this retrospective analysis. This lack of standardisation reflects real world clinical practice but may have biased our findings in patients with shorter or longer CT follow up intervals. Whilst the ideal study would have rigorous protocol-led control of serial CT and functional measurements and antifibrotic use, no such study yet exists and were it to begin today, outcome data may only be available several years hence. Accordingly, we believe our analyses capture a realistic contemporary cross-section of IPF data points.

In conclusion, we have demonstrated for the first time that change in a computer-derived variable, vessel-related structures, which has no visual correlate is a powerful surrogate for mortality in IPF. VRS change correlates weakly with FVC change and identifies different poor-outcome patients than a ≥10% FVC decline threshold. Use of a VRS threshold of ≥0.40% change alongside a ≥10% FVC decline threshold can identify 30% more patients that reach an endpoint and argues for the consideration of VRS change as an IPF drug trial co-endpoint to adjudicate indeterminate FVC declines of 5.0–9.9%.

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M. Kokosi has nothing to disclose. A. de Lauretis has nothing to disclose. E.P. Judge has nothing to disclose. T.M. Jacob has nothing to disclose. T. Peikert has nothing to disclose. R. Karwoski reports grants (paid to Mayo Clinic) from Royal Brompton Hospital, during the conduct of the study; royalties (paid to Mayo Clinic) from Imbio, LLC, outside the submitted work; and has a patent Systems and Methods for Analysing in vivo Tissue Volumes using Medical Imaging Data licensed to Imbio LLC. F. Maldonado has nothing to disclose. E. Renzoni reports personal fees for lectures from Roche and Takeda, personal fees for lectures and advisory board meetings from Boehringer, outside the submitted work. T.M. Maher is an investigator in an ongoing Phase 2b study for Gilead; reports grants and personal fees for advisory board work from GSK, personal fees from Boehringer Ingelheim InterMune, Lanthio, Sanofi Aventis, AstraZeneca, Roche, Bayer, Biogen Idec, Cipla, Prometic and Apellis, grants, personal fees and research fees (paid to institution) from UCB, outside the submitted work. A. Altmann has nothing to disclose. A.U. Wells reports personal fees for lectures and advisory board work from InterMune, Boehringer Ingelheim, Roche and Bayer, personal fees for advisory board work from Gilead and MSD, personal fees for lectures from Chiesi, outside the submitted work.

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References

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