Mobile spirometry as a digital marker of lung function

Poster No. 26

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Background

Patient data collected digitally via mobile devices are becoming an essential part of our lives and also might be helpful for disease management. Many digital devices allow patients to provide data away from clinical settings and with substantially higher frequency compared to data collected from in-clinic procedures.

In respiratory area, mobile devices to measure lung function outside of hospital environment on daily basis are becoming increasingly popular.

However, little guidance is available on the comparative analysis of mobile spirometry collected by patients at home and clinical spirometry collected by clinician at clinic. Furthermore, utility of the mobile spirometry data in clinical drug development is also of interest. The current practice is to compare the data visually via Bland Altman plots, which has limitations of descriptive rather than inferential technique and does not quantify differences between clinic and mobile spirometry to the extent that might be relevant for decision making.

We present the results of the post-hoc analysis of pre-dose lung function, Forced Expiratory Volume in 1 second, trough FEV1, which is a common regulatory endpoint in respiratory disease,.

Objectives

To investigate comparability of the trough FEV1 measurements collected with mobile spirometry device by a patient at home compared to data collected by a clinician during a clinic visit with respect to treatment effect.

Methods

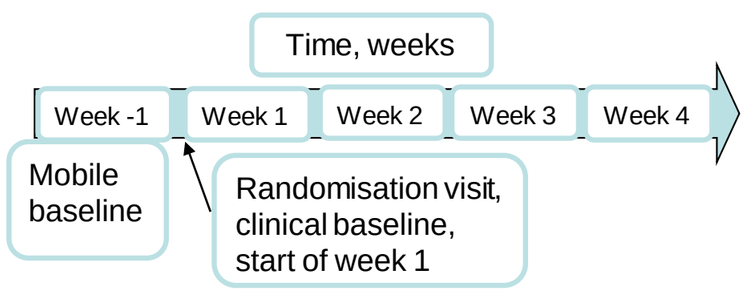
Data

- Trial 200699, randomised, parallel-group, double-blind trial in 338 randomised COPD patients with asthmatic component
- Dose-response Phase IIb with 6 treatment arms
- 4 week duration
- Treatment arms (coded): 0, 1, 4, 8, 16, 0 / other compound
- Endpoints:

  •$Clinic\ FEV1$ (trough) change from baseline measured at clinic visit (3 visits including randomisation)

  • $Mobile\ FEV1$ (trough) change from baseline measured daily at home by patients. Daily readings were averaged over weekly intervals to reduce noise pertinent to daily measurements. All available daily readings were used. Thus, mobile spirometry outcome was available at baseline and 4 time points after randomisation to compute a weekly average (Figure 1).

Figure 1. Baseline collection timelines



Device AM3, combined electronic home spirometer and diary, provided by eResearch Technology, Inc. (ERT) (Philadelphia, Pennsylvania, US), records daily lung function measured by patient at home, symptoms and rescue medication use.

Methods (continued)

Statistical Methods

Mixed effect joint models with correlated random effects

Each of the endpoints, mobile and clinic, was modelled via mixed effects modelling approach and combined in one model via correlated random effects (Fieuws and Verbeke, 2004)

For each person i and time j consider

•$Mobile\ FEV1_{ij} = X_{ij}\beta + \beta_T Treat + u1_i + \varepsilon 1_{ij}$

•$Clinic\ FEV1_{ij} = X_{ij}\gamma + \gamma_T Treat + u2_i + \varepsilon 2_{ij}$

$$u1_i, u2_i \sim N(0, \Sigma),$$
$$where\ \Sigma = \begin{pmatrix} \sigma_1 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2 \end{pmatrix}$$

Where X_{ij} are fixed-effect predictors (might vary between endpoints), $\varepsilon 1_{ij} \sim N(0, \tau_1^2)$, $\varepsilon 2_{ij} \sim N(0, \tau_2^2)$ and are independent of each other and of $u1_i$, $u2_i$.

Fixed effects: age, gender, baselines, smoking history, age first treated with inhaler, time (factor), treatment, time by treatment interaction, baseline by time interaction.

$Treat$ is a factor variable coding treatment arms, β_T is a vector of treatment effects detected by mobile spirometry and γ_T is a vector of treatment effects detected by clinic spirometry, hence estimation $\gamma_T - \beta_T$ and associated standard error is possible within the model.

Results

Compliance

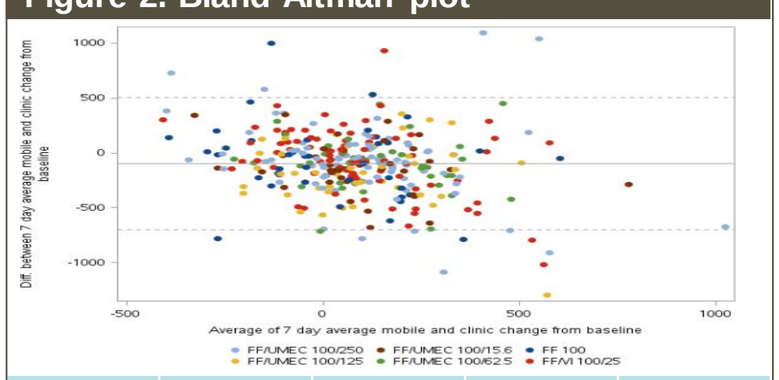
The compliance was very good with the predominant majority of patients providing at least 4 daily readings per week. 332 out of initial 338 patients records were available for analysis at the last week, out of these 332, only 4 patients provided fewer than 4 daily readings per the final week.

Differences between treatment effects estimates using mobile and clinic

The results presented correspond to the end of trial, i.e. the last clinic visit and the last week of mobile trough FEV1 (changes from baseline). Treatment effects estimated from the joint model are presented for each arm against FF, the active control arm

We contrast Bland Altman (BA) descriptive approach (Figure 2) with the quantified results obtained from applying the proposed modelling approach (Table 1). BA plot shows a difference between the endpoints (vertical axis), mobile minus clinic, against their mean (horizontal axis). It shows a substantial variation and an overall lower estimated mean for the mobile versus clinic measurements. Table 1 shows that the differences in estimation of treatment effect between mobile and clinic range from negligible to substantial and no consistent bias is evident. In three out of five comparisons mobile spirometry shows lower estimated treatment effect compared to clinic. After adjusting for covariates, treatment and time, the residual correlation between the random effects was 0.34 ($p<0.001$).

Figure 2. Bland Altman plot



Mean	SD	Median	Min	Max
-99	303	-91	-1298	1094

Results (continued)

Table 1. Treatments effect estimates (95%CI) and their differences from the joint model as measured by mobile and clinic spirometry

Treatment arm	N	Mobile	Clinic	Mobile - Clinic Difference, ml
		Treatment Effects, ml		
1	42	40 (-39, 118)	93 (5, 182)	-54 (-165, 58)
p-value		*0.323*	*0.039*	*0.345*
4	39	101 (21, 181)	142 (52, 232)	-41 (-154, 72)
p-value		*0.013*	*0.002*	*0.473*
8	45	31 (-46, 109)	122 (35, 209)	-91 (-200, 19)
p-value		*0.424*	*0.006*	*0.104*
16	83	100 (32, 168)	90 (13, 167)	10 (-86, 107)
p-value		*0.004*	*0.023*	*0.834*
0 / other compound	84	85 (17, 154)	74 (-3, 151)	11 (-85, 108)
p-value		*0.014*	*0.060*	*0.817*

Discussion

Model Benefits

The model performs joint estimation of treatment effects detected by mobile and clinic spirometry and adjusts for potential within-subject correlation between the two endpoints. Allowing for outcomes to be correlated through correlated random effects provides robust inference of model parameters.

This approach allows to quantify the difference in treatment effects and the difference in the effects of the other covariates on outcomes.

Model Limitations

This model might be too restrictive for longer trial durations where the correlations between further time points diminish with time. In this case, alternative covariance structures over time could be considered.

Utility

Mobile spirometry is being increasingly utilised in the clinical practice and is a promising tool in digital health technology area with a potential scope to be employed in virtual clinical trial settings and to monitor disease progression.

However, our results show that more research is required to understand the drivers behind the differences in clinic and mobile spirometry which might be related to specific respiratory conditions and active compounds/treatments as well as to the differences in how the two measures are taken (guided by a physician in the clinical vs. no guidance at home). Also, further investigations into predictive nature of this biomarker are warranted.

References

1. Fieuws and Verbeke, *STATISTICS IN MEDICINE*, 2004;23:3093–3104.

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