Digital home resources in clinical trial management

Marlies Wijsenbeek
Erasmus MC
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Digital home resources in clinical trial management
Experiences from the ILD field

• Why do we want home based measurements in trials?

• What have we learned so far?

• What are the challenges?
The patient with a progressive deadly disease, in need for better treatments

Idiopathic Pulmonary Fibrosis

Included with permission of patient

Jürgen Behr et al. Eur Respir J 2020;56:1902279
Outcomes of clinical trials should reflect how a patient feels, functions and survives

Most used endpoints in pulmonary studies:

• Lungfunction
• Patient reported outcomes
• 6 minute walk test
• Accelerometry
• Imaging
• Blood biomarkers
• Acute exacerbations/ hospitalisations
• Treatment failure
Trial design & endpoints

>12 visits in 12 months

<table>
<thead>
<tr>
<th>Visit</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>6a</th>
<th>7</th>
<th>7a</th>
<th>8a</th>
<th>9</th>
<th>EOT</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+4</td>
</tr>
<tr>
<td>Time window</td>
<td>Before or at the latest at visit 1</td>
<td>1</td>
<td>15</td>
<td>29</td>
<td>43</td>
<td>58</td>
<td>127</td>
<td>160</td>
<td>211</td>
<td>253</td>
<td>309</td>
<td>365</td>
<td>+28</td>
</tr>
</tbody>
</table>

Informed consent X
HRCT test to central review
Demographics X
Medical history X
Adverse events, concomitant medication X
Inclusion criteria X
Inclusion criteria X
Physical examination, vital signs X

Only 6 visits really require presence in the hospital

Access to studies may be an issue

- Travel distance to specialised centres
- Dependence on oxygen supplementation
- Energy limitations
- Hesitant to burden family
- COVID-19 impact
- Too much time in the hospital

*Included with permission of patient*
Another problem: we need more patients or longer trials to find and effect of treatments

Many new trials have smaller margins to detect changes

The example of IPF

The natural decline in FVC in IPF
200 ml/year

FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; N, nintedanib; P, pirfenidone
Another problem: we need more patients or longer trials to find and effect of treatments.

Many new trials have smaller margins to detect changes.

The on "anti-fibrotics" decline in FVC in IPF 100 ml/year.

FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; N, nintedanib; P, pirfenidone
Another problem: we need more patients or longer trials to find and effect of treatments

Many new trials have smaller margins to detect changes

- More patients
- Longer trials
- More measurements

The example of IPF

The current margin for a new drug: 50 ml
Many new trials have smaller margins to detect changes

Sample size estimates to achieve 80% power, comparing intermittent and repeated measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect size</th>
<th>Measurement frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Weekly × 24</td>
</tr>
<tr>
<td>FVC; assumed control change of -50 mL</td>
<td>20</td>
<td>5946</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>1942</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>951</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; N, nintedanib; P, pirfenidone
Why want home based measurements in trials:

- Inclusion
- Access to care
- Real time monitoring
- Stimulate Compliance
- Safety Monitoring
- Symptoms
- Patient filled registers
- Expand number of measurement
- Reduce number of Patients needed
- Less burden COVID-19 proof
- Patient as partner in Research
Digital home resources in clinical trial management
Experiences from the ILD field

• Why do we want home based measurements in trials?

• What have we learned so far?

• What are the challenges?
Digital home resources used in clinical trials in ILD

Included with permission of both patients
FVC home monitoring enables patient-tailored detection of decline

FVC, forced vital capacity
Home spirometry is reliable

Russell et al\(^1\)

![Scatter plot showing the correlation between office and home FVC readings.](image)

- **Mean Difference (Hospital - Home)**
  - **Average FVC (L)**
  - **Mean Difference (Hospital - Home)**

Marcoux et al\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office FVC (L) – mean (SD)</td>
<td>2.77 (0.82)</td>
<td>2.70 (0.77)</td>
<td>2.76 (0.77)</td>
<td>2.70 (0.82)</td>
</tr>
<tr>
<td>Home FVC (L) – mean (SD)</td>
<td>2.70 (0.82)</td>
<td>2.63 (0.77)</td>
<td>2.48 (0.55)</td>
<td>2.45 (0.54)</td>
</tr>
</tbody>
</table>

**Correlation between office and home-held FVC, r (95% CI)**

- 0.97 (0.92, 0.99)*
- 0.96 (0.90, 0.98)*
- 0.93 (0.81, 0.97)*
- 0.90 (0.75, 0.96)*

Moor et al\(^3\)

- **Relative variability home FVC: 3.8% (3–12%)**
- **Median (SD) home FVC: 0.13 L (0.05–0.39 L)**
- **Home and hospital FVC highly correlated (r=0.94, P<0.001)**

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Data presented are Spearman correlations and 95% CI based on Fisher’s Z transformation.*P<0.0001. CI, confidence interval; FVC, forced vital capacity; SD, standard deviation.

Our experience – home monitoring system developed together with patients

**Patient**
- Sends real-time data to the platform
- Overview of results
- Information library
- Low threshold communication

- Automated email reminders

**Healthcare provider**
Direct access to patient data:
- Enables real-time detection of change in FVC and PROs
- Alarm settings on FVC and adverse effects
- Reduces missing data in trials

- Automated email alerts

FVC, forced vital capacity; PRO, patient-reported outcome
Moor CC et al. Am J Respir Crit Care Med 2020;202;393–401
Primary endpoint: change in K-BILD total score after 24 weeks

Higher K-BILD total score corresponds with better health-related quality of life. K-BILD, King’s Brief Interstitial Lung Disease; MCID, minimal clinically important difference.

Moor CC et al. Am J Respir Crit Care Med 2020;202;393–401
Patient experiences were positive

PATIENT EXPERIENCES HOME MONITORING

95%  Recommend to others
89%  Better insights disease course
88%  Feels more secure
87%  Lower threshold communication

Moor CC et al. Am J Respir Crit Care Med 2020;202;393–401
Home monitoring allowed for close and reliable monitoring of disease course

- Mean (SD) within-patient variability of FVC was 5.2% (1.7)
- Strong correlation at all time points
  - $(r \geq 0.96, P < 0.001)$
- Slopes of home and hospital FVC over time were comparable

FVC, forced vital capacity; SD, standard deviation
Moor CC et al. Am J Respir Crit Care Med 2020;202;393–401
Multicenter studies may experience more FVC variability in individual patients

*Blue lines depict ordinary least squares fit to in-clinic measurements. FVC, forced vital capacity
Swigris JJ et al. Eur Respir J 2019;54;PA1333
Median FVC predicted change from baseline at week 24 measured with home spirometry in the ITT analysis set (n=253)

Low number of measures impacts the calculation of individual predictions of 24-week changes; statistical analysis methods impact results

FVC, forced vital capacity; ILD, interstitial lung disease; ITT, intention-to-treat
Pulse-oximetry: use expanded in COVID-19 pandemic

Home monitoring post-SARS-COV-19 infection: HOMECOMIN’ project

Patient-reported and recorded outcomes

unpublished data
Explorative use of surrogates of the 6 MWT at home

Steps per day predicts mortality similar to 6MWT

Sit-to-Stand test correlates well with 6MWT

Stanford–Apple collaboration 6 MWT at home

Bahmer T et al. BMC Pulmonary Medicine 2017; 17:104
Fedi A et al. Respiration april 2021
STARLINER study

Daily home spirometry and accelerometry during peridiagnostic period
Patients with IPF experienced greater declines in FVC compared with patients with non-IPF ILD

Semi-annual changes in FVC during the peri-diagnostic period*

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Home/site measurement</th>
<th>Statistical analysis model</th>
<th>IPF</th>
<th>Non-IPF ILD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in FVC, mL</td>
<td>Home</td>
<td>Linear regression</td>
<td>−167.7 (−441.3, 132.3)**</td>
<td>−25.3 (−272.9, 103.9)†</td>
</tr>
<tr>
<td>Change in FVC, mL</td>
<td>Site</td>
<td>Linear regression</td>
<td>−188.2 (−426.1, 85.4)‡</td>
<td>−23.4 (−127.7, 115.5)‡</td>
</tr>
</tbody>
</table>

Individual courses of home spirometry and accelerometry for:

A patient with IPF

A patient with non-IPF ILD

*Excluding patients with <30 days of data; **n=42; †n=47; ‡n=46; Interim data. FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

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Experiences from the ILD field

• Why do we want home based measurements in trials?

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Adherence to home spirometry over time

INMARK® trial; Mean adherence 86% over 52 weeks, median adherence 96%

Adherence was calculated as the number of weeks that a subject provided ≥1 measurement divided by the number of weeks that they were followed in the trial. Analysis was based on the total number of subjects who were still followed in the trial within the time period.
Diurnal variation in FVC

Results of DIVA study

FVC-morning was significantly higher than FVC-afternoon (mean difference: 36 mL, \(P<0.001\))

No diurnal variation was found for FEV1 (7 mL, \(P=0.35\))

Differences in FVC cannot be fully explained by activity just before the measurement

FEV1, forced expiratory volume in one second; FVC, forced vital capacity
Moor CC. ERJ Open Res 2020;6:00054-2020
Measurement variability and technical issues
Realtime feedback to center AND patient improves quality

Strong correlation at all time points ($r \geq 0.96, P < 0.001$)
Slopes of home and hospital FVC over time were comparable

Artificial Intelligence (AI) for Quality Control of Home Spirometry data

• AI methods\(^1,2\) can perform the artefact detection usually done by trained technicians in centralized clinical trials

• AI methods to provide real-time quality feedback with equivalent accuracy to manual over-reading\(^3\)

• Further validation currently ongoing

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Slide courtesy of ArtiQ
Need for consensus on the method for handling missing data and outliers in the statistical analysis

Sensitivity analyses for mean and median 24-week FVC change measured using home spirometry

Pre-specified analysis of the primary endpoint in a 24-week, double-blind, randomized controlled trial of pirfenidone vs. placebo in patients with uILD was impossible due to physiologically implausible FVC values caused by:

- Problems with the technical reliability of the recorded home spirometry values and variability in patients’ skill levels in operating the spirometers
- Inclusion of patients with a small number of readings collected over a short observation period, leading to extrapolation of short-term variations across the 24-week treatment period

Three sensitivity analyses were performed to exclude the following subgroups:

1. **ITT population (N = 253)**
   - 127 patients
   - 126 patients

2. **Subset A**
   - Patients who had changes in FVC from baseline below ~1000 mL and above +1000 mL

3. **Subset B**
   - Patients who had <3 site spirometry measurements indicating observation periods of <8 weeks

4. **Subset C**
   - Patients who had <10% of expected home spirometry observations

CI, confidence interval; FVC, forced vital capacity; ITT, intention-to-treat; uILD, unclassifiable interstitial lung disease

Maher TM et al. Am J Respir Crit Care Med 2020;201:A2575
And other challenges

• Optimal frequency of measurements?
• Optimal alarm settings?
• Promoting equal access to trials or not?
• Fit for all patients and doctors?
• How about other wearables / sensors?
• Ready as endpoint?
• ....

Conclusion: Digital home resources in clinical trial management

• Why: allows for closer monitoring at lower burden for patients, reduces trial size and makes patients a partner in research

• What we learned: home based spirometry and PRO collection is feasible, reliable and highly appreciated by patients. More data needed also on other outcomes

• Which challenges: technical and analytical, as well as impact on patient and outcomes when longterm used
A big thank you

To all the patients that helped us through the years

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To the ILD_team

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Boehringer Ingelheim

Roche

Erasmus MC Foundation

Erasmus MC
Thank you!

To learn more about a homemonitoring application and patient experiences scan the QR code.