Falls as outcome in clinical trials

Jörg Goldhahn, Niklas König

Falls have significant impact on affected individuals. They may lead to injuries including fractures, hospitalization, decreased mobility, and loss of independence. Therefore, falls constitute a relevant outcome parameter in clinical trials. However, especially elderly and frail patients may forget to report or neglect falls. The use of fall-detection technology in clinical trials may overcome this challenge. However, commercially-available fall-detection technologies are designed as personal emergency response systems rather than as measurement tools to assess the effects of an intervention. Hence, before adopting a commercially-available fall-detection technology in a clinical trial one has to assess its suitability for such application.
Falls as outcome in clinical trials

J Goldhahn, MD, MAS
Director, Musculoskeletal Translational Medicine NIBR Basel
Lecturer at ETH Zurich

Niklas König
Translational Fellow, ETH Zurich

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Content

From accident to endpoint

- Motivation
  - Consequences of falls
  - Causes

- Definitions

- Falls as endpoint in clinical studies
  - Relevance
  - Current approaches
  - New approaches
  - Requirements for new technology
  - First results

Conclusions
Motivation

Consequences on an individual level

- None
- Pain
- Fear of falling
- Contusion(s)
- Muscle injuries
- Fracture(s)
- Decrease in mobility
- Loss of independance
- Direct or indirect leading to death
Motivation

Consequences on an individual level

Increased risk of falling

Fall

Fear of falling

Muscle atrophy

Decrease in mobility

Motivation

Consequences on a population level

- Patients with muscle weakness have a 5-fold increased risk for falls

- Injurious falls are drivers for next fracture, re-hospitalization and health care utilization
  - Between 8.6% and 25.5% health care utilization after falls
  - Mean cost of injurious falls at emergency department $11,408
Global years lived with disability (YLDs) ranks with 95% uncertainty intervals (UI) for the 25 most common causes in 1990 and 2010. Vos et al. Lancet 2012

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mean rank (95% UI)</th>
<th>1990</th>
<th>2010</th>
<th>% change (95% UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Low back pain</td>
<td>1.3 (1 to 3)</td>
<td>1.1 (1 to 2)</td>
<td>43 (34 to 53)</td>
<td></td>
</tr>
<tr>
<td>2 Major depressive disorder</td>
<td>2.2 (1 to 3)</td>
<td>1.9 (1 to 3)</td>
<td>37 (25 to 50)</td>
<td></td>
</tr>
<tr>
<td>3 Iron-deficiency anaemia</td>
<td>2.5 (1 to 3)</td>
<td>3.3 (2 to 6)</td>
<td>-1 (-3 to 2)</td>
<td></td>
</tr>
<tr>
<td>4 Neck pain</td>
<td>4.4 (4 to 7)</td>
<td>4.3 (3 to 7)</td>
<td>41 (28 to 55)</td>
<td></td>
</tr>
<tr>
<td>5 COPD</td>
<td>6.0 (4 to 8)</td>
<td>5.8 (3 to 10)</td>
<td>46 (32 to 62)</td>
<td></td>
</tr>
<tr>
<td>6 Other musculoskeletal disorders</td>
<td>6.1 (4 to 9)</td>
<td>5.9 (4 to 8)</td>
<td>45 (38 to 51)</td>
<td></td>
</tr>
<tr>
<td>7 Anxiety disorders</td>
<td>6.2 (3 to 15)</td>
<td>6.4 (4 to 9)</td>
<td>37 (25 to 50)</td>
<td></td>
</tr>
<tr>
<td>8 Migraine</td>
<td>8.7 (6 to 15)</td>
<td>8.9 (5 to 15)</td>
<td>40 (31 to 51)</td>
<td></td>
</tr>
<tr>
<td>9 Diabetes</td>
<td>10.0 (7 to 14)</td>
<td>9.1 (6 to 13)</td>
<td>68 (56 to 81)</td>
<td></td>
</tr>
<tr>
<td>10 Falls</td>
<td>10.1 (7 to 14)</td>
<td>10.1 (7 to 14)</td>
<td>46 (30 to 64)</td>
<td></td>
</tr>
<tr>
<td>11 Osteoarthritis</td>
<td>11.0 (11 to 21)</td>
<td>12.3 (9 to 17)</td>
<td>64 (50 to 79)</td>
<td></td>
</tr>
<tr>
<td>12 Drug use disorders</td>
<td>12.2 (6 to 19)</td>
<td>12.5 (9 to 16)</td>
<td>40 (27 to 54)</td>
<td></td>
</tr>
<tr>
<td>13 Hearing loss</td>
<td>14.0 (9 to 19)</td>
<td>13.5 (7 to 20)</td>
<td>29 (22 to 36)</td>
<td></td>
</tr>
<tr>
<td>14 Asthma</td>
<td>14.9 (10 to 21)</td>
<td>15.3 (10 to 20)</td>
<td>28 (21 to 34)</td>
<td></td>
</tr>
<tr>
<td>15 Alcohol use disorders</td>
<td>15.0 (11 to 21)</td>
<td>15.8 (12 to 21)</td>
<td>32 (16 to 50)</td>
<td></td>
</tr>
<tr>
<td>16 Road injury</td>
<td>15.2 (11 to 20)</td>
<td>16.0 (9 to 22)</td>
<td>48 (37 to 60)</td>
<td></td>
</tr>
<tr>
<td>17 Bipolar disorder</td>
<td>17.1 (9 to 25)</td>
<td>16.1 (12 to 20)</td>
<td>30 (13 to 49)</td>
<td></td>
</tr>
<tr>
<td>18 Schizophrenia</td>
<td>17.1 (9 to 24)</td>
<td>16.6 (9 to 23)</td>
<td>41 (31 to 51)</td>
<td></td>
</tr>
<tr>
<td>19 Dysthymia</td>
<td>19.5 (12 to 27)</td>
<td>18.6 (13 to 26)</td>
<td>41 (34 to 48)</td>
<td></td>
</tr>
<tr>
<td>20 Epilepsy</td>
<td>19.8 (13 to 25)</td>
<td>21.8 (18 to 27)</td>
<td>36 (27 to 47)</td>
<td></td>
</tr>
<tr>
<td>21 Ischaemic heart disease</td>
<td>22.2 (13 to 35)</td>
<td>21.9 (17 to 29)</td>
<td>48 (40 to 57)</td>
<td></td>
</tr>
<tr>
<td>22 Epilepsy</td>
<td>22.7 (19 to 28)</td>
<td>22.3 (16 to 35)</td>
<td>29 (19 to 39)</td>
<td></td>
</tr>
<tr>
<td>23 Tuberculosis</td>
<td>23.9 (18 to 32)</td>
<td>23.1 (19 to 28)</td>
<td>5 (1 to 11)</td>
<td></td>
</tr>
<tr>
<td>24 Ischaemic heart disease</td>
<td>24.5 (19 to 34)</td>
<td>24.3 (16 to 35)</td>
<td>29 (19 to 39)</td>
<td></td>
</tr>
<tr>
<td>25 Neonatal encephalopathy</td>
<td>25.3 (21 to 33)</td>
<td>25.8 (21 to 33)</td>
<td>80 (71 to 88)</td>
<td></td>
</tr>
<tr>
<td>26 Tuberculosis</td>
<td>26.0 (20 to 35)</td>
<td>26.3 (20 to 35)</td>
<td>84 (48 to 120)</td>
<td></td>
</tr>
</tbody>
</table>
## Motivation

### Causes

<table>
<thead>
<tr>
<th>Risk Factor Variable</th>
<th>Unadjusted</th>
<th>p</th>
<th>Adjusted*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional LE weakness</td>
<td>4.00 (1.30–5.84)</td>
<td>&lt;0.0001</td>
<td>5.21 (2.22–12.22)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BBS score (&lt;50/56)</td>
<td>2.44 (1.18–4.28)</td>
<td>0.008</td>
<td>4.12 (1.32–12.80)</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of prescription medications (≥4)</td>
<td>1.40 (0.70–2.92)</td>
<td>0.38</td>
<td>1.31 (0.63–2.75)</td>
<td>0.47</td>
</tr>
<tr>
<td>Number of risk factors score (per unit increase in score)</td>
<td>1.73 (1.14–2.62)</td>
<td>0.01</td>
<td>2.00 (1.13–3.56)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CII confidence interval; LE lower extremity; BBS Berg Balance Scale

* Adjusted for age, gender, and treatment arm of the Project to Prevent Falls in Veterans study

† Sum of dichotomous variables: balance impairment (BBS score <50/56), functional LE weakness (unable to stand up from chair without using the arms of the chair), and number of prescription medications (≤4)

Fall definitions I

*components*

- Topographic description
- Biomechanical description
- Exclusion criteria
- Behavioural description
Fall definitions II

descriptors

“coming to rest on the floor”

“loss of balance”
“resulting from tripping”

“excessive alcohol consumption”

“unintentionally”
“unexpected”
Fall definitions III

Example I

“A fall is an event which results in a person coming to rest inadvertently on the ground or other lower level and other than as a consequence of the following: Sustaining a violent blow, loss of consciousness, sudden onset of paralysis, as in a stroke or an epileptic seizure.”

(Kellogg Work Group, 1987)
“A fall was defined as losing your balance such that your hands, arms, knees, buttocks or body touch or hit the ground or floor.”

(Berg, 1997)
Fall definitions VI
Automated fall detection

Topographic description

Biomechanical description

Exclusion criteria

Behavioural description
Fall definitions VII

Example actibelt

“...an unintentional change in position where the elder ends up on the floor or ground.”

(Canadian Institute for Health Information, 2002)

1. Impact assumption
2. Orientation assumption
3. Rest period
A fall was defined as losing your balance such that your hands, arms, knees, buttocks or body touch or hit the ground or floor.”

(Berg, 1997)

1. Impact assumption
2. Orientation assumption
3. Rest period
A fall should be defined as an unexpected event in which the person comes to rest on the ground, floor, or lower level.

Fall in clinical studies

Relevance

- Meaningful for patients
- Accepted by health authorities
- Associated with care, treatment and costs
- Quantifiable
Fall in clinical studies

Current approaches (subjective vs. Objective)

- Weight – patient reported or scales?
- Falls – patient reported or automatic fall detection?
  - Patients tend to forget or neglect falls
  - Recall issues, particularly among older patients
- Activity – patient reported or automatic recording?
  - Patients overestimate activity after intervention
  - PRO biased by expectation/ mental status
## Fall in clinical studies

### New approaches

<table>
<thead>
<tr>
<th>Measurement principle</th>
<th>Analytical challenges</th>
<th>Clinical challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accelero-metry</strong></td>
<td>Algorithms, thresholds</td>
<td>Compliance</td>
</tr>
<tr>
<td>Triaxial acceleration</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Floor detection</strong></td>
<td>Algorithms, thresholds</td>
<td>Limited clinical use</td>
</tr>
<tr>
<td>Ground reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Video-optic systems</strong></td>
<td>Image processing algorithms</td>
<td>Limited clinical use privacy</td>
</tr>
<tr>
<td>Motion detection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Barometric</strong></td>
<td>Algorithms, thresholds</td>
<td>Compliance</td>
</tr>
<tr>
<td>Sudden pressure change</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combinations</strong></td>
<td>Combinatio n of sensors</td>
<td>Compliance</td>
</tr>
<tr>
<td>Acceleration and barometric measure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fall in clinical studies

New approaches - challenges

- High Variability of fall characteristics
- Highly variable environment
Fall in clinical studies

New approaches - challenges

- Actibelt (Trium, Germany)
- Lifeline (Philips, Nederland)
- PAMSys (Biosensics, USA)
- LifeMonitor (Equivital, UK)
- Senso (Realtime, Ireland)
- Vitalbase (Tunstall, UK)
- VitalLink (Choice Medical Alert, USA)
- GoSafe (Philips, Nederland)
- Vigi’fall (Vigilio, France)
- Sapphire (APDM, USA)
- Shimmer (Realtime, Ireland)

On the market

Not ready

Still for research

No one validated for falls detection

Is available fall-detection technology suitable for use in clinical trials? Shyamal Patel, Alessandro Puiatti, Jim Niemi, Ronenn Roubenoff, Joerg Goldhahn, Paolo Bonato ICFSR 2014 - International Conference on Frailty & Sarcopenia Research
1. **Analytical validation = measurement validation study (exploratory stage)**

- Establish performance characteristics
  - Sensitivity: needs to be as high as possible to reduce the risk of underestimation
  - Specificity: needs to be as high as possible to reduce the risk of overestimation. Situations that could lead to false positives should be though trough based on the device mechanism and tested accordingly
  - Repeatability/reproducibility: N/A

- What is acceptable in terms of performance thresholds needs to be agreed with HAs.

- Analytical validation could be considered in a controlled setting e.g. lab setting

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2. Clinical performance study

- Subjects should reflect the target population for the device (age, sex, ethnicity)

- Comparative study with paired design:
  - New device vs falls reported per patients (disuse phase II)
  - New device vs falls observed by caregivers – could be explored in a nursing home setting

- Sponsors should consult with FDA prior to planning a study
Analytical validation

Statistics

External observation, diary

<table>
<thead>
<tr>
<th>Condition as determined by Gold standard</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>True</td>
<td>False positive</td>
</tr>
<tr>
<td>False</td>
<td>True negative</td>
</tr>
</tbody>
</table>

- \( \text{True positive} \)
- \( \text{False positive} \)
- \( \text{False negative} \)
- \( \text{True negative} \)

\( \rightarrow \) Positive predictive value or Precision
\( \rightarrow \) Negative predictive value

\( \downarrow \) Sensitivity or recall
\( \downarrow \) Specificity (or its complement, Fall-Out)

\( \text{Accuracy} \)

\[
\text{sensitivity} = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false negatives}}
\]

\[
\text{specificity} = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}}
\]

\[
\text{accuracy} = \frac{\text{number of true positives} + \text{number of true negatives}}{\text{number of true positives} + \text{false positives} + \text{false negatives} + \text{true negatives}}
\]

\( \text{Compliance impact} [\%] = 1 - \left( \frac{\text{Sensitivity [\%]}}{\text{Compliance Sensitivity [\%]}} \right) \times 100 \)
Additional information to be provided to regulators

- **How** and why the device works
- **User skills** level and **training**
  - Patients
  - Site staff
- **Human factors** considerations
- **Safety** of the device
- **Data** management
  - Data privacy
  - Version control
Conclusions

- Large need for automated fall detection
- Technology available
- Has to meet clinical requirements
- Should be validated
- Patient compliance critical
- → next presentation
Thank you for your attention