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, decrase in 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 challenges. 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-availablefall-detection technology in a clinical trial one has to assess its suitability for such application.

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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

1st Winter Symposium of "The Human Motion Project"

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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

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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

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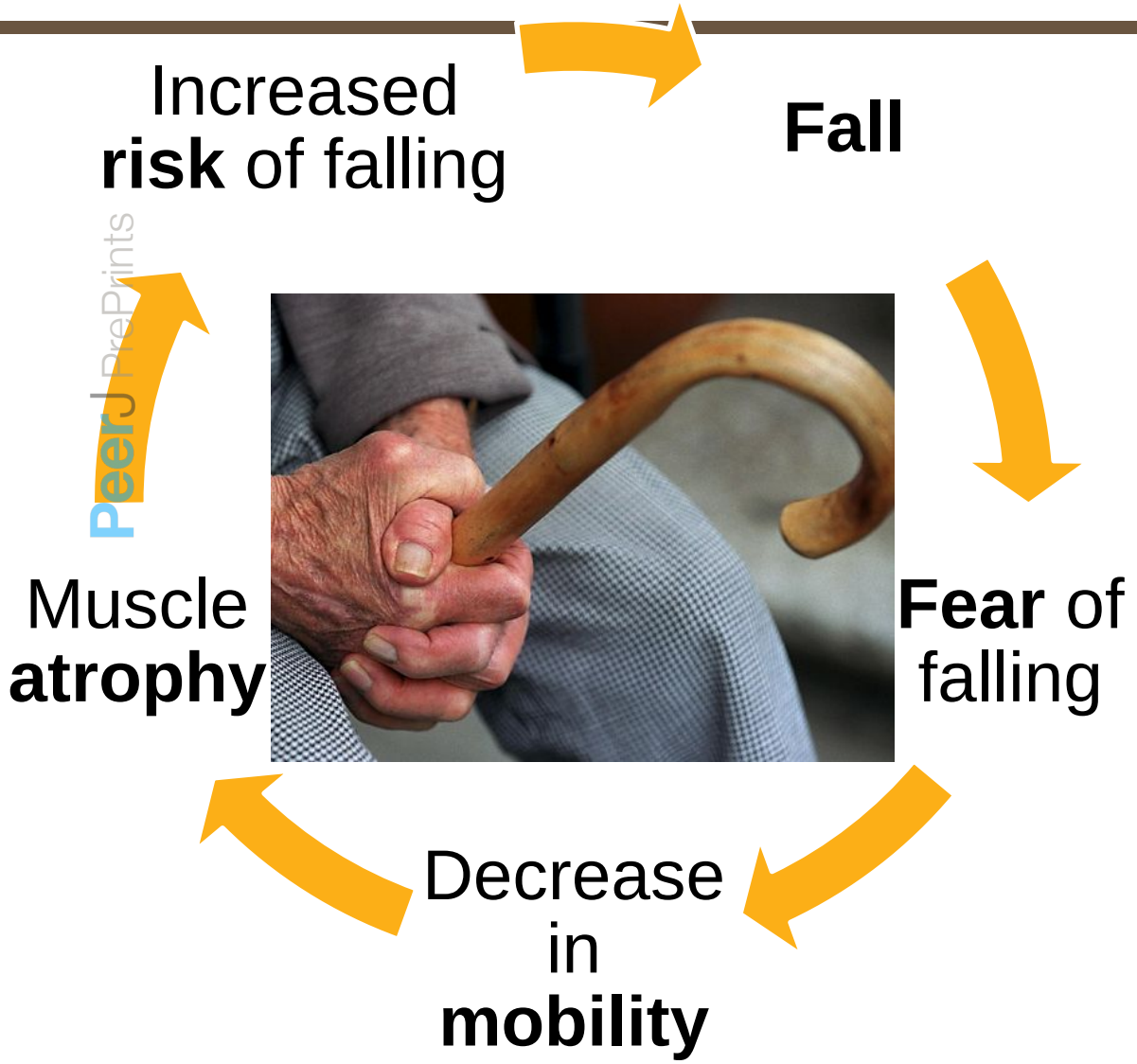
Motivation

Consequences on an individual level



Vellas BJ, Wayne SJ, Romero LJ, Baumgartner RN, Garry PJ. Fear of falling and restriction of mobility in elderly fallers. Age Ageing. 1997 May;26(3):189-93.

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Motivation

Consequences on a population level

- Patients with muscle weakness have a 5-fold increased risk for falls
  - *Moreland JD et al. J Am Geriatr Soc. 2004 Jul;52(7):1121-9.*
  - *L. Rubenstein. Age Ageing (September 2006) 35 (suppl 2): ii37-ii41.*
- 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
    - *Schwenk M et al. BMC Med Res Methodol. 2012 Apr 17;12:50.*
    - *Woolcott JC et al. Osteoporos Int. 2012 May;23(5):1513-9.*

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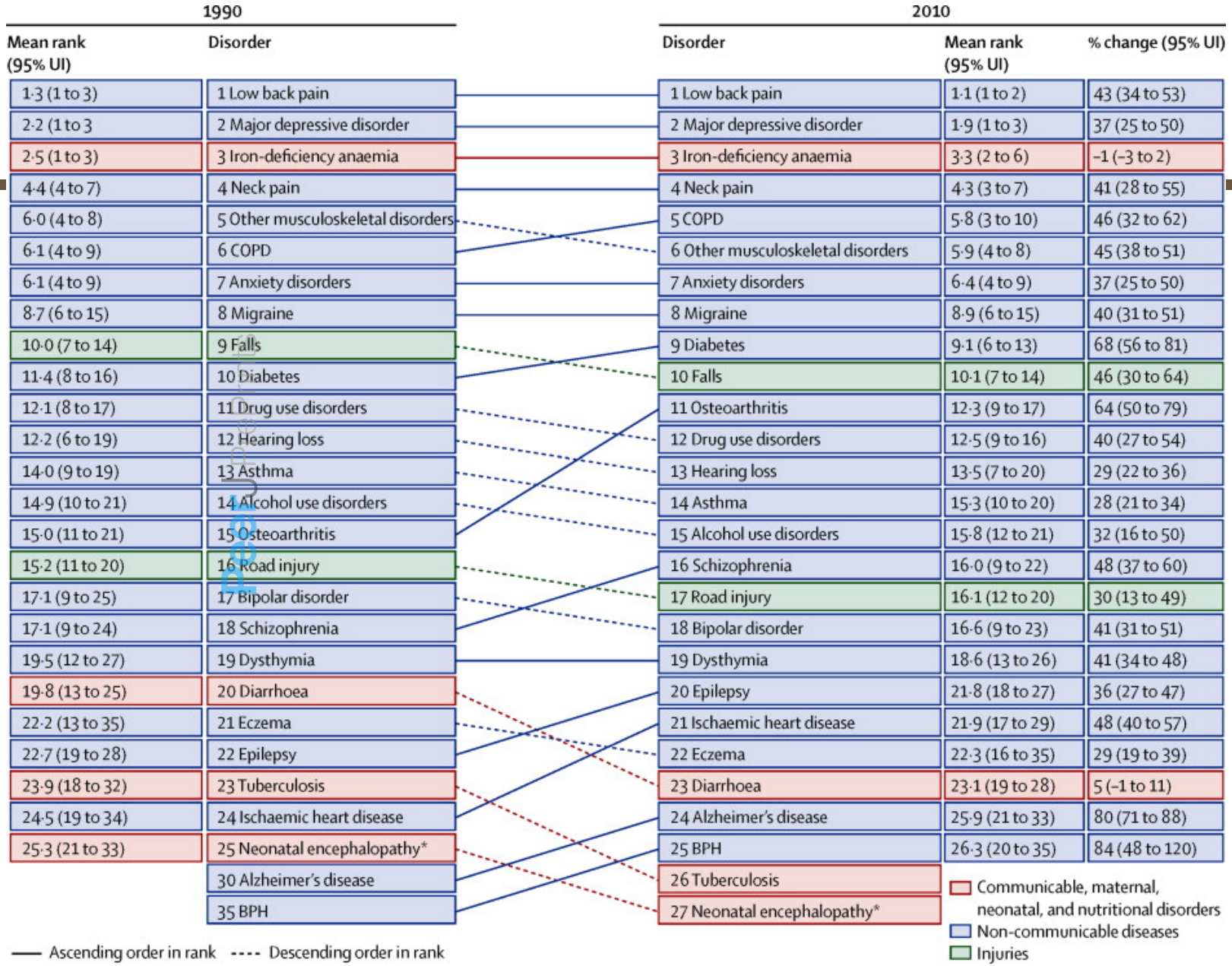

Global years lived with disability (YLDs) ranks with 95% uncertainty intervals (UI) for the 25 most common causes in 1990 and 2010. Vos et al. Lancet 2012

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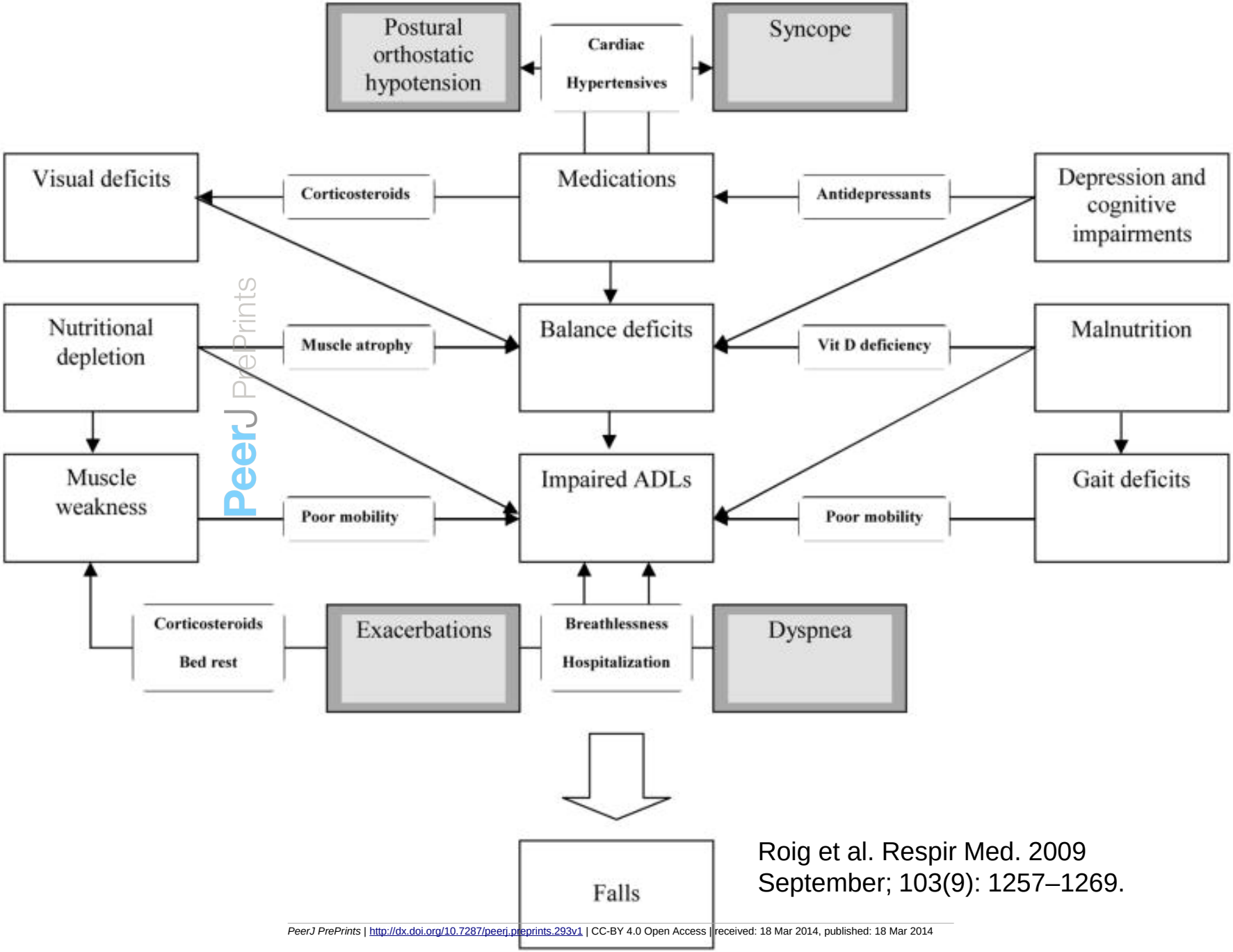

Roig et al. Respir Med. 2009 September; 103(9): 1257–1269.

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Motivation

Causes

Risk Factor Variable	*Relative Risk for Falling Over 12 Months (95% CI)*			
	Unadjusted	p	*Adjusted**	p
Functional LE weakness	4.00 (1.30–5.84)	< 0.0001	5.21 (2.22–12.22)	0.0001
BBS score (< 50/56)	2.44 (1.18–4.28)	0.008	4.12 (1.32–12.80)	0.01
Number of prescription medications (≥ 4)	1.40 (0.70–2.92)	0.38	1.31 (0.63–2.75)	0.47
Number of risk factors scored† (per unit increase in score)	1.73 (1.14–2.62)	0.01	2.00 (1.13–3.56)	0.02

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 (b4)

Muir et al. Physiother Can. 2010 Fall; 62(4): 358–367

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Fall definitions I

components

Topographic description

Biomechanical description

Exclusion criteria

Behavioural description

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Fall definitions II

descriptors

"coming to rest on the floor"

"loss of balance"

"resulting from tripping"

"excessive alcohol consumption"

"unintentionally"

"unexpected"

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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)

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Fall definitions IV

"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)

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Fall definitions

Assessment tool questionnaire

Topographic description

Biomechanical description

Exclusion criteria

Behavioural description

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Fall definitions VI

Automated fall detection

Topographic description

Biomechanical description

Exclusion criteria

Behavioural description

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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

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Fall definitions VIII

Example actibelt

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

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Fall definition

Recommendation ProFaNE and FARSEEING

A fall should be defined as an unexpected event in which the person comes to rest on the ground, floor, or lower level

Klenk et al. Z Gerontol Geriat 2013 · 46:720–726
Lamb SE et al. J Am Geriatr Soc 53:1618–1622

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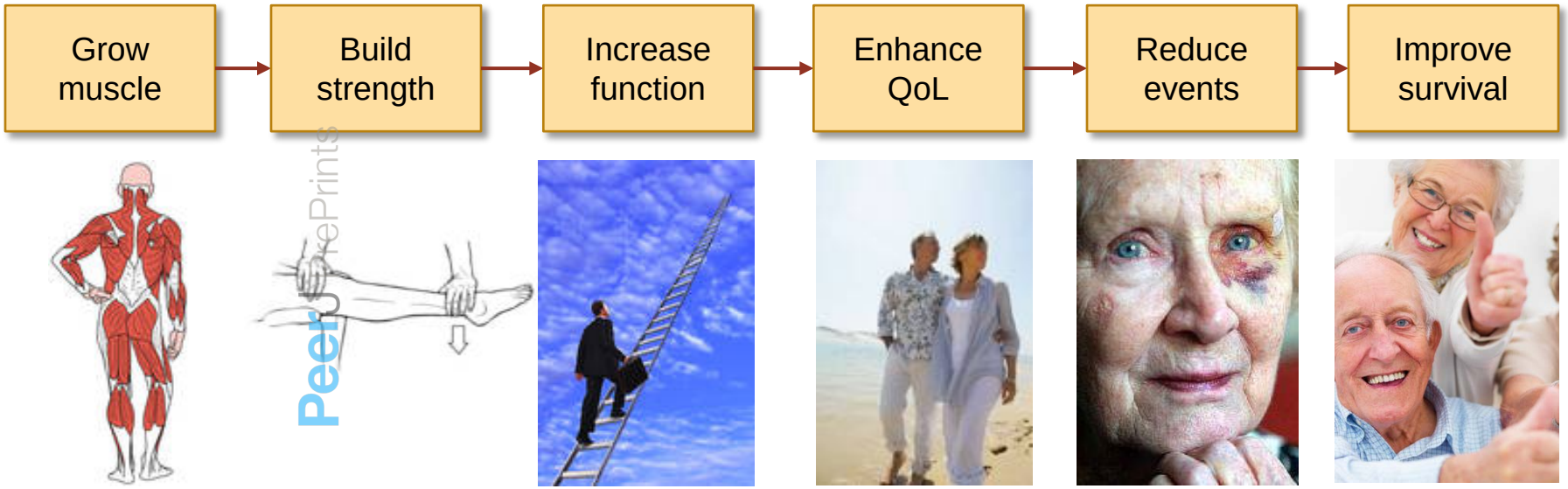
Fall in clinical studies

Relevance



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

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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

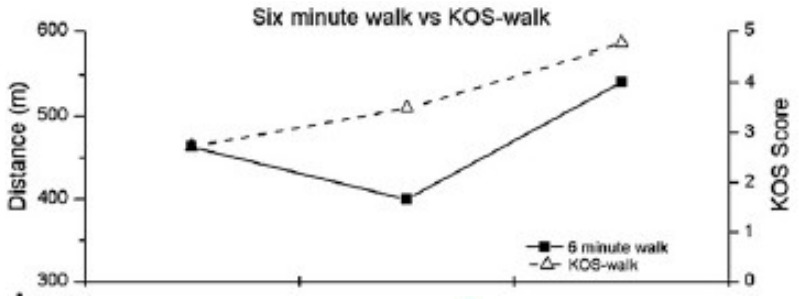
    Cummings SR, et al. Forgetting falls. The limited accuracy of recall of falls in the elderly. J Am Geriatr Soc. 1988 Jul;36(7):613-6.
    Mackenzie L et al. Validation of self-reported fall events in intervention studies. Clin Rehabil. 2006 Apr;20(4):331-9.

    Recall issues, particularly among older patients

    Ganz DA et al.. Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. J Am Geriatr Soc. 2005 Dec;53(12):2190-4.
- Activity – patient reported or automatic recording?
  - Patients overestimate activity after intervention

    Mitzner et al. Measuring Functional Improvement After Total Knee Arthroplasty Requires Both Performance- Based and Patient-Report Assessments The Journal of Arthroplasty Vol. 26 No. 5 2011
  - PRO biased by expectation/ mental status

    Simmen BR et al., Goldhahn J. Development of a predictive model for estimating the probability of treatment success one year after total shoulder replacement - cohort study. Osteoarthritis Cartilage. 2008 May;16(5):631-4.



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Fall in clinical studies

New approaches

	Measurement principle	Analytical challenges	Clinical challenges
Accelero-metry	Triaxial acceleration	Algorithms, thresholds	Compliance
Floor detection	Ground reaction	Algorithms, thresholds	Limited clinical use
Video-optic systems	Motion detection	Image processing algorithms	Limited clinical use privacy
Baro-metric	Sudden pressure change	Algorithms, thresholds	Compliance
Combi-nations	Acceleration and barometric measure	Combinatio n of sensors	Compliance

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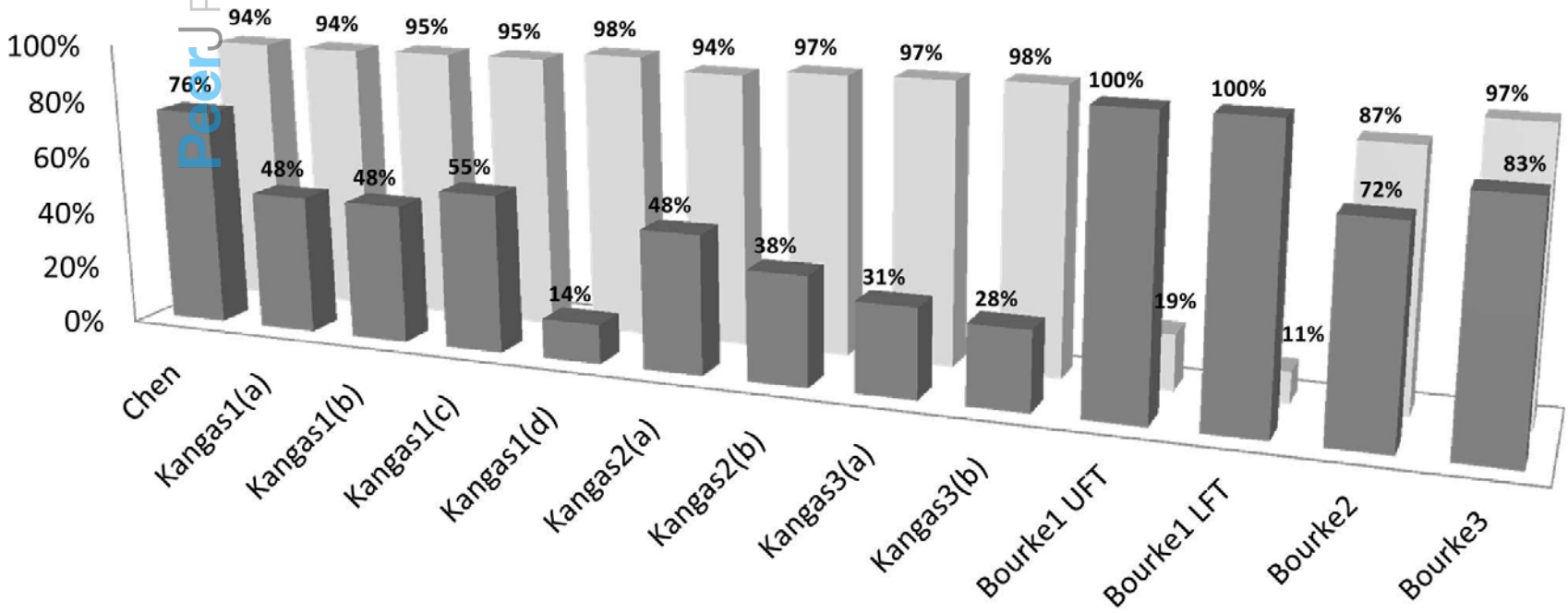
Fall in clinical studies

New approaches - challenges

- High Variability of fall characteristics
- Highly variable environment



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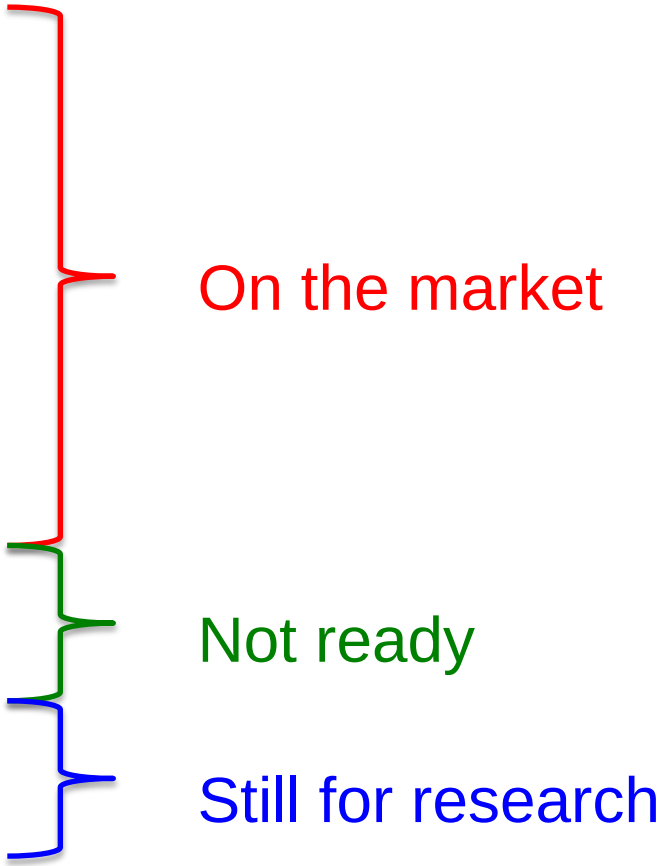
Fall in clinical studies

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)



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

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How to validate a fall measuring device – Best guess (1/2)

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

SCENARIOS FOR THE EVALUATION OF FALL DETECTORS

Category	Name	Outcome
Backward fall (both legs straight or with knee flexion)	Ending sitting	Positive
	Ending lying	Positive
	Ending in lateral position	Positive
	With recovery	Negative
Forward fall	On the knees	Positive
	With forward arm protection	Positive
	Ending lying flat	Positive
	With rotation, ending in the lateral right position	Positive
	With rotation, ending in the lateral to the left position	Positive
	With recovery	Negative
Lateral fall to the right	Ending lying flat	Positive
	With recovery	Negative
Lateral fall to the left	Ending lying flat	Positive
	With recovery	Negative
Syncope	Vertical slipping against a wall finishing in sitting position	Negative
Neutral	To sit down on a chair then to stand up (consider the height of the chair)	Negative
	To lie down on the bed then to rise up	Negative
	Walk a few meters	Negative
	To bend down, catch something on the floor, then to rise up	Negative
	To cough or sneeze	Negative

Noury et al. Proceedings of the 29th Annual International Conference of the IEEE EMBS Cité Internationale, Lyon, France August 23-26, 2007.

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How to validate a fall measuring device – Best guess (2/2)

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

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Analytical validation

Statistics

External observation, diary

device

		Condition as determined by *Gold* standard		
		True	False	
Test outcome	Positive	True positive	False positive	→ Positive predictive value or Precision
	Negative	False negative	True negative	→ Negative predictive value
		↓ Sensitivity or recall	↓ Specificity (or its complement, Fall-Out)	Accuracy

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

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

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

$$\textit{Compliance impact}\ [\%] = 1 - \left(\frac{\textit{Sensitivity}\ [\%]}{\textit{Compliance Sensitivity}\ [\%]}\right) * 100$$

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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

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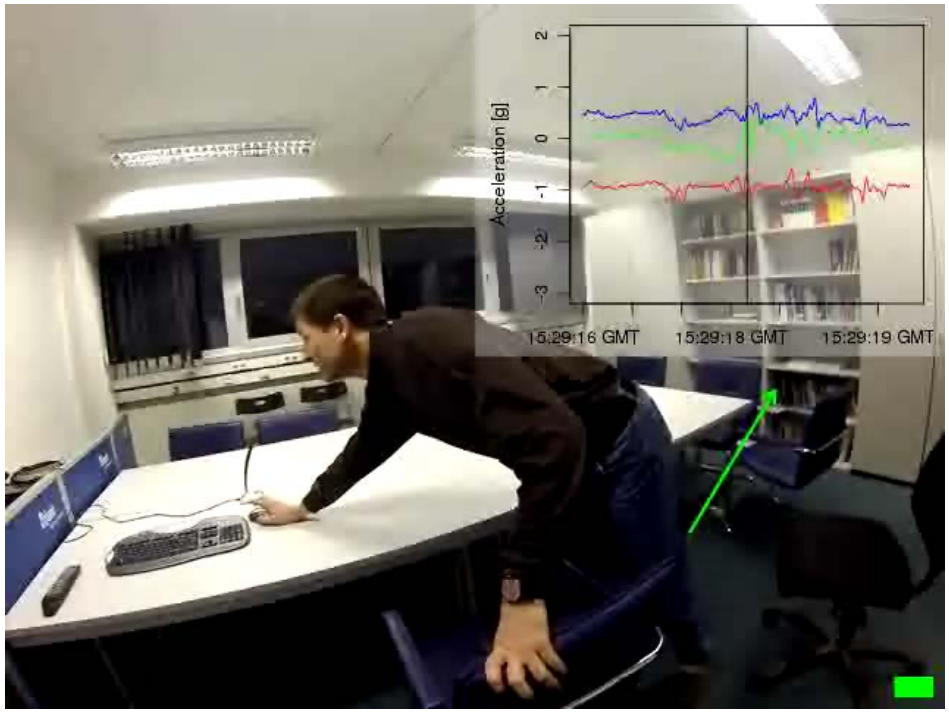
Conclusions

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



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