CHAPTER 9

Epilogue
The C-Mill is an instrumented treadmill augmented with projected environmental context, which has been designed for the assessment and training of walking, in particular in the context of rehabilitation. The aim of this thesis was to examine the usability, validity and efficacy of the C-Mill for providing a task-specific assessment and training of walking, with a specific focus on walking adaptability. In this chapter, the potential of the C-Mill for assessing and training walking adaptability will be discussed, the assumptions underlying adaptability treadmill training will be evaluated, and directions for future research will be described within the continuum of translational research.

**Translational research**

Translation refers to the process of turning a basic science discovery into a practical application, and ultimately into an improvement of public health [1, 2]. Although these two steps have been seen as different aspects of the translation process (e.g., [2]), this process is best viewed in terms of a continuum [1]. The biomedical research translation continuum [1] is shown in Figure 9.1, which depicts the entire trajectory from a basic science discovery to improved public health. Four practical landmarks are distinguished in the progression of knowledge, which are separated by “translation chasms” requiring translation activities to progress to the next stage on the translation continuum [1]. In what follows, past, current and required future steps regarding the assessment and training of walking adaptability using the C-Mill will be mapped onto this continuum and its chasms.

![Biomedical research translation continuum from a basic science discovery to public health impact (adapted from Drolet and Lorenzi [1]). Findings at any stage feed back to previous research stages (dashed line), resulting in further examination and action.](image_url)

**Figure 9.1**
The process of translation starts with a basic science discovery, which is considered in the context of a potential practical application to bridge the first translation chasm (Figure 9.1). The development of the C-Mill was inspired by the finding that walking adaptability is reduced in different populations [3-14], which is associated with increased fall risk [3, 15-17] but may be intervenable [15, 18, 19]. The ability to adjust walking in response to environmental demands therefore seems to be an essential part of both the assessment of walking ability and fall risk and interventions aimed at improving these essential aspects of walking. This is consistent with previous recommendations that dynamic, attention-demanding and challenging tests are needed for the assessment of walking [20, 21], and to include the complex and hazardous situations of everyday walking requiring step adjustments in intervention programs [22, 23]. The development of the C-Mill for training walking adaptability was motivated further by the basic science discovery that training should focus on task-specific practice with great amounts of movement practice and performance feedback [24-26]. Defining this “best practice” is one of the first and crucial steps in translational research [27]. It forms the foundation of the practical application and without a sound and firm understanding of what should be assessed or trained in practice according to research-based evidence, it is impossible to measure the gap between “desired” and “actual” care [27].

An overview of the translation continuum applied to the C-Mill is presented in Table 9.1. The studies in this thesis focused primarily on the second translation chasm with the aim to progress to a proven clinical application of the C-Mill (Figure 9.1). Therefore, the validity of the C-Mill for the assessment of walking adaptability will be discussed in the next session, followed by a section on the safety, practicability and efficacy of the C-Mill in the training of walking adaptability. The third and last translation chasm is bridged when clinical practices and guidelines are implemented and adopted, with the ultimate aim to impact public health (Figure 9.1). The translation activities required to achieve such public health impact using the C-Mill are discussed in the final section Future directions and considerations.

The C-Mill for assessing walking adaptability

The C-Mill was designed to elicit step adjustments during treadmill walking by projecting visual context on the treadmill surface. This visual context may be based on the individual’s walking pattern and may thus be movement-dependent, enabling
Table 9.1 The biomedical research translation continuum applied to the C-Mill. The research in this thesis focuses on the second translation chasm (T2). Therefore, the landmarks and chasms after T2 are shaded.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Inquiry and Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic Science Discovery</strong></td>
<td>Walking adaptability is reduced in different populations with increased fall risk, but may be reversible.</td>
</tr>
<tr>
<td></td>
<td>Task-specificity, great amounts of movement practice and feedback on performance are important principles of effective rehabilitation</td>
</tr>
<tr>
<td>T1</td>
<td>Translation of basic science to application in humans</td>
</tr>
<tr>
<td>Proposed Human Application</td>
<td>Can the C-Mill be used to objectively assess walking adaptability?</td>
</tr>
<tr>
<td></td>
<td>Can the C-Mill be used to improve walking adaptability and reduce fall incidence in different fall-prone populations?</td>
</tr>
<tr>
<td>T2</td>
<td>Translation to clinical application</td>
</tr>
<tr>
<td>Proven Clinical Application</td>
<td>The C-Mill can be effectively used for the assessment and training of walking adaptability</td>
</tr>
<tr>
<td></td>
<td>How do we get physicians and physical therapists to use the C-Mill in clinical practice?</td>
</tr>
<tr>
<td>T3</td>
<td>Translation to practice</td>
</tr>
<tr>
<td>Clinical Practice</td>
<td>Assessment and training of walking adaptability using the C-Mill in well-defined target groups</td>
</tr>
<tr>
<td></td>
<td>Does the C-Mill correctly identify persons with reduced walking adaptability in clinical practice?</td>
</tr>
<tr>
<td></td>
<td>Does C-Mill adaptability treadmill training improve safe everyday walking, participation and reduce fall incidence?</td>
</tr>
<tr>
<td>**</td>
<td>Practice Based Research</td>
</tr>
<tr>
<td></td>
<td>Practice-based research networks; patient registries, cohort and case-control studies, meta-analysis</td>
</tr>
<tr>
<td>Public Health Impact</td>
<td>Established standard of care: C-Mill can be used to assess and train walking adaptability, leading to improved safe everyday walking, participation and reduced fall incidence</td>
</tr>
<tr>
<td></td>
<td>Can we improve any part of our treatment pathway?</td>
</tr>
<tr>
<td>**</td>
<td>Continual practice improvement</td>
</tr>
<tr>
<td></td>
<td>Findings in any stage feedback to previous research stages (dashed line) for further examination and action.</td>
</tr>
</tbody>
</table>
step adjustments in a well-controlled and challenging individual-specific manner. Chapter 2 focused on the assessment of walking adaptability using the C-Mill in persons with a transtibial amputation, persons with a transfemoral amputation and, able-bodied persons. The aim of this study was to test the face validity and construct validity of a treadmill-based protocol for objectively assessing walking adaptability, a necessary step towards a proven clinical application of the C-Mill in the assessment of walking adaptability (Figure 9.1 and Table 9.1, second translation chasm). Participants performed an anticipatory and reactive obstacle avoidance task as well as a visually guided stepping task involving a sequence of stepping targets with varying regularity. Inferior walking adaptability scores were found for the transfemoral group, intermediate scores for the transtibial group and superior scores for the control group, underscoring the face validity of the protocol in question. The sensitivity of the protocol was supported in that obstacle avoidance success rates decreased when fewer steps were available for obstacle avoidance (reducing the available response time) and stepping accuracy decreased with increased pattern irregularity. The C-Mill thus seemed useful for the assessment of walking adaptability and was therefore used in several other studies in different target groups as well as in more fundamental studies on a variety of aspects that play a role in step adjustments during walking [12, 28-35]. For example, the C-Mill was used to study the attentional costs of visually guided walking [12, 29, 34], response inhibition during obstacle avoidance [28, 32], the effect of visually guided stepping on comfortable walking speed [30], and step adjustments as a function of the direction of target shifts [33].

In addition to the observation that walking adaptability can be assessed with the C-Mill, the walking adaptability assessment described in Chapter 2 appeared to cover a different construct than the standard clinical gait and balance tests. Moderate significant correlations between walking adaptability scores and timed walking test outcomes were found only for anticipatory obstacle avoidance success rates and not for reactive obstacle avoidance success rates and accuracy of stepping. This finding indicated that the latter two walking adaptability scores quantified a unique, complementary aspect of walking ability, likely related to the ability to make online walking adjustments under time pressure. Similar results were found when analyzing the relation between the standard clinical gait and balance tests used in Chapter 4 and the laboratory treadmill-based obstacle avoidance task used in Chapter 5; weak non-significant correlations were observed between the standard clinical gait and balance tests and the challenging, time-constrained obstacle avoidance task at post-test (all $r<0.490$, $p>0.05$, suggesting
The studies in the present thesis thus showed that the challenging, time-constrained walking adaptability tests cover a unique construct of walking ability and support recent suggestions that dynamic, attention-demanding and challenging tests are required to assess and detect mobility and balance deficits in higher functional but vulnerable populations [20, 21]. The C-Mill seems to be quite capable of providing such assessments given its asset of enriching the walking surface with challenging movement-dependent visual context.

Although the walking adaptability tests used in Chapter 2 proved to capture a unique aspect of walking ability, it is noteworthy that the differences observed between the groups were only significant between the transfemoral amputation group and the control group for obstacle avoidance performance. This was the case for both anticipatory obstacle avoidance and reactive obstacle avoidance, implying that the differences between groups were not more pronounced for reactive obstacle avoidance than for anticipatory obstacle avoidance, as was expected from previous research [3-5, 9, 10]. The effect of walking speed may explain this discrepancy. Participants performed the walking adaptability test at a self-selected preferred treadmill speed, which was significantly lower in the transfemoral amputation group (2.3 km/h) than in the transtibial amputation group (3.3 km/h) and the control group (3.8 km/h). The supplementary material of Chapter 2 (page 40-42) revealed that a decrease in walking speed positively affected walking adaptability scores for stepping accuracy and reactive obstacle avoidance performance in the control group. The performance on these tasks may thus have been overestimated in both amputation groups due to the lower walking speeds observed in these groups, the transfemoral amputation group in particular. Another reason for the absence of significant differences in walking adaptability scores between the transtibial amputation group and both other groups may be that not all persons with a lower limb amputation necessarily have poor walking ability. The point of view that limitations in walking ability are directly linked to medical status seems outdated [36], because there is typically much variation within (patient) groups, ranging from poor to good walking ability. This was also observed in Chapter 2, in which large within-group variations in both walking adaptability scores and standard clinical walking test scores were found. Therefore, a generic test of functional walking ability without floor or ceiling effects is needed, which may be provided by the C-Mill.

The technology underlying the C-Mill offers opportunities for challenging, time-constrained walking adaptability assessments without using body markers. The walking adaptability scores obtained using the C-Mill indicated adequate face
validity and added unique information to the commonly used timed walking tests. However, more research is needed to close the second translation chasm and progress to a proven clinical application of the C-Mill in the assessment of walking adaptability, as will be discussed further in the section Future directions and considerations.

C-Mill for training walking adaptability

As in pertinent literature [3-14], the studies in this thesis showed impaired walking adaptability in different fall-prone populations (i.e., persons with lower limb amputation – Chapter 2, persons in the chronic stage after stroke – Chapter 5, older adults with a fall-related hip fracture – Chapter 8). However, training of walking adaptability, and certainly C-Mill adaptability treadmill training, is only in its infancy. It is therefore useful to discuss the potential of C-Mill adaptability treadmill training for improving walking adaptability and reducing fall risk, as will be done later in this chapter.

Assumptions underlying adaptability treadmill training evaluated

Studies on health care quality have consistently shown that actual practice is less consistent with evidence-based recommendations than deemed acceptable [27]. Monitoring this gap is an important aspect of translational research. Chapters 5 and 7 of this thesis evaluated the validity of the theoretical principles underlying C-Mill adaptability treadmill training as identified in the first translation chasm (Figure 9.1 and Table 9.1). C-Mill adaptability treadmill training derives from the basic scientific findings and insights suggesting that intervention programs should be task specific, evoke great amounts of movement practice, provide feedback on performance and incorporate the practice of step adjustments in challenging environments (Table 9.1) [22-26]. In Chapter 5, the validity of the assumption of task-specific practice underlying adaptability treadmill training was evaluated. It was found that after 5-6 weeks of adaptability treadmill training the obstacle avoidance success rate improved significantly by 25% in persons in the chronic stage after stroke. Furthermore, the associated walking adjustments required less attention, as evidenced by the improved performance on the concurrent Stroop task. The observed improvements in obstacle-avoidance success rate and Stroop performance were strongly correlated, indicating specific rather than non-specific improvements. In addition, task-specific improvements in dynamic balance and target stepping were reported in Chapter 4. These task-specific improvements
corroborated the assumptions regarding effective training underlying adaptability treadmill training.

Chapter 7 focused on the validity of the second assumption underlying adaptability treadmill training, the amount of walking practice. In this chapter, the number of steps performed per training session was compared between adaptability treadmill training, conventional treadmill training and usual physical therapy in older adults with a recent fall-related hip fracture. As expected, the number of steps performed during conventional treadmill training was significantly greater than during usual physical therapy, as was the case for adaptability treadmill training with projected visual context. In fact, more than twice as many steps were performed during treadmill-based training sessions than during usual physical therapy sessions.

Adaptability treadmill training thus conformed to its assumptions regarding task-specific practice and amount of movement practice, bridging the first translation chasm to a proposed clinical application of the C-Mill. However, whether this will actually result in an effective clinical application demands studies in the second translation chasm (Figure 9.1 and Table 9.1), as will be discussed below, starting with the safety and practicability (usability) of adaptability treadmill training.

Safety and practicability of adaptability treadmill training (usability)

Exploring the usability of the proposed practical application in terms of safety and practicability is an important aspect of the second translation chasm (Figure 9.1 and Table 9.1). Collectively, the studies contained in this thesis indicate that participants were generally able to successfully and safely perform the adaptability exercises on the C-Mill. Chapters 4 and 5 revealed that no adverse events were reported apart from occasional muscle soreness after the first adaptability treadmill training sessions; one participant dropped out due to aggravated lumbago during the sessions. Although Chapter 7 reported mild discomfort during and after adaptability treadmill training sessions, this was not different from conventional treadmill training sessions or sessions of usual physical therapy, and formed no reason to withdraw from participation. Moreover, no serious adverse events related to the intervention occurred in the group of frail older adults described in this chapter. The results of the implementation project described in Chapter 3 showed that adaptability treadmill training was largely successful in terms of practicability in different patient populations and in persons with varying levels of walking ability. Importantly, in all studies presented in this thesis, despite the absence of a safety
harness not a single fall occurred during the adaptability treadmill training sessions (or other training sessions for that matter). Consistent with this fact, Hollands et al. [37] reported that adaptability treadmill training is safe and feasible to deliver in outpatient stroke physiotherapy services; also in this study no adverse events were reported while none of the participants withdrew because the treatment was unacceptable [37]. Similar results were reported in a study involving persons with degenerative cerebellar ataxia, who all completed the adaptability treadmill training program without any adverse events [38]. Adaptability treadmill training thus appears safe and practicable to deliver in different patient populations.

The studies in this thesis further showed that adaptability treadmill training is well accepted by persons in the chronic stage after stroke as well as by older adults with a recent fall-related hip fracture. Chapter 4 reported that all participants, who were in the chronic stage after stroke, were enthusiastic about adaptability treadmill training and would recommend it to peers. These results are consistent with those found in Chapter 7 for older adults with a recent fall-related hip fracture. The latter chapter focused specifically on the attitude of older adults towards adaptability treadmill training as well as conventional treadmill training and usual physical therapy, and showed that all three types of training were rated as useful, motivating, fun, challenging and enjoyable. In addition, the participants considered conventional and adaptability treadmill training relevant for older adults and would recommend it to peers, as in Chapter 4. In accordance with these results, adaptability treadmill training was much appreciated by persons with degenerative cerebellar ataxia [38]. Adaptability treadmill training thus appeared not only usable in terms of safety and practicability, but was also well appreciated by different patient groups, which is a prerequisite for interventions to be effective in general [39, 40] and C-Mill adaptability treadmill training in particular, as will be discussed next.

**Efficacy of adaptability treadmill training**

In Chapter 4 significant improvements were reported in different clinical gait and balance tests after 5-6 weeks of adaptability treadmill training, including the 10 meter walk test, the obstacle subtask of the Emory functional ambulation profile, the timed Up-and-Go test and the Berg Balance scale. In addition, the success rates on the laboratory Target-Stepping Task (during stance) improved in all but one condition and participants were more active as evidenced by the increased number of steps performed daily in the week after completion of the adaptability treadmill training program than in the week before the program. Chapter 5 showed that these
improvements were accompanied by a 25% improvement in obstacle avoidance success rate and decreased associated attentional demands as evidenced by improved Stroop success rates during the obstacle avoidance maneuver. Interestingly, the relative improvement was markedly greater for the most challenging and task-specific outcomes than for the standard clinical gait and balance outcomes. The average relative improvement was 47% for the obstacle avoidance success rates (from 52% at pretest to 77% at posttest) and 23% for the Stroop success rates during obstacle avoidance (from 63% at pretest to 78% at posttest), whereas these percentages varied only between 3 and 14% for the standard clinical gait and balance tests. These results underscore the importance of including the task-specific and challenging outcome measures implied by the training construct. In fact, Fonteyn et al. [38] showed significant improvements in obstacle avoidance success rates and the obstacle subtask of the Emory functional ambulation profile after 5 weeks of adaptability treadmill training in persons with degenerative cerebellar ataxia, but not in the standard clinical tests of walking and balance, including the Berg Balance Scale, the timed Up-and-Go test, and the 10 meter walk test. Moreover, the change in obstacle avoidance success rates observed in Chapter 5 was not significantly related to changes in any of the standard clinical gait and balance test scores observed in Chapter 4, whereas changes in the three timed walking tests (10 meter walk test, timed Up-and-Go test and obstacle subtask of the Emory functional ambulation profile) showed significant moderate to strong correlations with each other (Table 9.2). This implies that participants who improved well in obstacle avoidance performance did not necessarily improved well on the 10 meter walk test, timed Up-and-Go test and obstacle subtask of the Emory functional ambulation profile. Again, these results indicate that the obstacle avoidance task exploited in Chapter 5 and the standard clinical gait tests administered in Chapter 4 cover different, complementary constructs of walking ability, which both appeared to improve after only 10 sessions of adaptability treadmill training in persons in the chronic stage after stroke.

Chapters 4 and 5 presented promising results regarding the efficacy of adaptability treadmill training. Although the studies described in these chapters did not include a control group, the 25% improvement in obstacle avoidance performance was more than twice as large as previously reported improvements with other task-specific gait-training interventions using the same laboratory obstacle avoidance task. Van Swigchem et al. [41] reported an 8% improvement in obstacle avoidance performance with functional electrical stimulation of the lower-
Epilogue

Table 9.2 Correlations between the pre-posttest differences in obstacle avoidance success rates and standard clinical gait and balance test scores.

<table>
<thead>
<tr>
<th></th>
<th>Δ OA success rate</th>
<th>Δ 10MWT</th>
<th>Δ TUG</th>
<th>Δ EFAP</th>
<th>Δ TIS</th>
<th>Δ BBS</th>
<th>Δ ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ OA success rate</td>
<td>1c</td>
<td>1c</td>
<td>0.625</td>
<td>0.720</td>
<td>0.008d</td>
<td>0.096</td>
<td>0.292</td>
</tr>
<tr>
<td>Δ 10MWT</td>
<td>-0.242c</td>
<td>1</td>
<td>0.625</td>
<td>0.720</td>
<td>0.008d</td>
<td>0.096</td>
<td>0.292</td>
</tr>
<tr>
<td>Δ TUGa</td>
<td>-0.357c</td>
<td>0.625</td>
<td>1</td>
<td>0.550</td>
<td>0.013d</td>
<td>0.315</td>
<td>0.425</td>
</tr>
<tr>
<td>Δ EFAP</td>
<td>-0.047c</td>
<td>0.720</td>
<td>0.550</td>
<td>1</td>
<td>0.102d</td>
<td>0.124</td>
<td>0.497</td>
</tr>
<tr>
<td>Δ TIS total</td>
<td>0.467b</td>
<td>0.008d</td>
<td>0.013d</td>
<td>0.102d</td>
<td>1d</td>
<td>0.378d</td>
<td>0.110d</td>
</tr>
<tr>
<td>Δ BBSa</td>
<td>0.113c</td>
<td>0.096</td>
<td>0.315</td>
<td>0.124</td>
<td>0.378d</td>
<td>1</td>
<td>0.076</td>
</tr>
<tr>
<td>Δ ABC</td>
<td>-0.191c</td>
<td>0.292</td>
<td>0.425</td>
<td>0.497</td>
<td>0.110d</td>
<td>0.076</td>
<td>1</td>
</tr>
</tbody>
</table>

Correlations (Pearson and a Spearman’s rho) between pretest-posttest differences (Δ) of obstacle avoidance (OA) success rates (average score over single and dual task conditions) and standard clinical balance and gait tests (n=15, b n=12, c n=13, d n=14). Significant correlations (p<0.05) are presented in bold. 10MWT: 10 meter walk test, TUG: timed Up-and-Go, EFAP: obstacle sub-task of the Emory functional ambulation profile, TIS: trunk impairment scale, BBS: Berg balance scale, ABC: activities-specific confidence scale.

Limb muscles compared to an ankle-foot orthosis in persons with a drop foot due to stroke, while Weerdesteyn et al. [15] observed a 12% improvement in fall prone older adults after 5 weeks of overground fall-prevention training. The latter improvement was significantly higher than the 6% improvement observed in the inactive control group and was accompanied by a significant reduction in fall incidence during a one-year follow-up, which was absent in the inactive control group [15]. This suggests that improvements on the obstacle avoidance task, as observed in Chapter 5, may translate to daily life. The finding reported in Chapter 4 that participants significantly improved their level of daily physical activity by 1,126 steps (i.e., 19%) after adaptability treadmill training is interesting in that regard and also suggests that the improvements after adaptability treadmill training may carry over to daily life activities. Given that step activity seems related to walking speed and balance [42, 43], the increased number of steps per day indicates that the observed improvements in walking speed and balance may translate to improvements in daily life. Moreover, even small increments in daily step activity are likely related to health improvements [44, 45], which highlights the importance of improving daily activity, especially in the sample under study which can be labeled as low active given their daily step activity (5,738 steps per day in the study presented in Chapter 4) [44]. Although the results described in Chapters 4 and 5 are
promising, future randomized controlled trials with multiple follow-up measurements are necessary to determine whether adaptability treadmill training indeed leads to improvements in participation and safe community walking. A recently published research protocol by Timmermans et al. [46] describes the design of such a randomized controlled trial on walking adaptability training after stroke. This trial is currently ongoing and will compare the effect of C-Mill adaptability treadmill training and an overground walking adaptability program for improving walking speed and walking adaptability at multiple follow-up measurements [46].

In Chapter 8 of this thesis, a randomized controlled trial with multiple follow-up measurements on the efficacy of adaptability treadmill training in older adults with a fall related hip fracture is presented. In this study, the efficacy of 6 weeks of adaptability treadmill training, conventional treadmill training and usual physical therapy was compared in terms of walking ability, fear of falling and fall incidence. The results showed that measures of walking ability, fear of falling and general health all improved over time in a similar fashion for adaptability treadmill training, conventional treadmill training and usual physical therapy. Significant group differences were only found for the Functional Ambulation Category and the dual-task effect on walking speed, which were in favor of conventional treadmill training and adaptability treadmill training, respectively. However, overall, no compelling evidence was found that adaptability or conventional treadmill training is more effective in improving walking ability and reducing fear of falling and fall incidence than usual physical therapy. Additional post hoc subgroup analyses, with stratification for pre-fracture tolerated walking distance and executive function, revealed several intervention effects that were generally in favor of adaptability and conventional treadmill training, indicating superiority over usual physical therapy for certain subgroups.

Although the subgroup analyses were performed post hoc, they had a plausible rationale and fitted well within the second translation chasm. As shown in Chapter 7, the treadmill-based training sessions evoked more than twice as many steps than the usual physical therapy sessions. This led to the idea that the two treadmill-based interventions might be more effective than usual physical therapy for participants with lower compared to higher walking activity prior to hip fracture, which was explored using pre-fracture tolerated walking distance for subgroup stratification. Notably, walking adaptability strongly relies on cortical control [47], which incited the exploration of executive function as a possible effect modifier; in particular, adaptability treadmill training might be more effective than conventional
treadmill training and usual physical therapy for participants with lower compared to higher executive function. Although the results of the subgroup analyses were largely consistent with these expectations, future randomized controlled trials with pre-specified and plausible subgroups, large(r) sample sizes, and interaction tests are needed to confirm pre-fracture tolerated walking distance and executive function as effect modifiers for adaptability treadmill training in order to identify those patients responding best to adaptability treadmill training [48].

Regarding the efficacy of adaptability treadmill training, the studies in the present thesis showed that adaptability treadmill training is a promising intervention for improving safe community ambulation in persons in the chronic stage after stroke, which had similar effects as conventional treadmill training and usual physical therapy on walking ability, fear of falling and fall incidence in older adults with a recent fall-related hip fracture. Adaptability and conventional treadmill training may be more effective compared to usual physical therapy in certain subgroups of older adults with a fall-related hip fracture. Overall, the studies in this thesis constitute a step forward on the long road of translational research; more research is necessary to confidently bridge the second translation chasm to a proven clinical application. Some specific directions and considerations in that regard will be discussed next.

**Future directions and considerations**

In this section, future directions and considerations of C-Mill research are discussed within the context of the associated stage of translation, starting with continual practice improvement, and followed by the second and third translation chasm (Figure 9.1 and Table 9.1).

**Continual practice improvement**

Continual practice improvement refers to findings at any stage that feed back to previous stages resulting in further examination and action (dashed line in Figure 9.1 and Table 9.1) [1]. For example, the C-Mill’s software and therapist-friendliness have been improved based on the experiences of the therapists who provided the adaptability treadmill training sessions in our studies, which was possible due to the unique collaboration within this project with the producer of the C-Mill (ForceLink, Culemborg, the Netherlands, now part of Motekforce Link, Amsterdam, the Netherlands). Although the studies in this thesis showed promising results for the C-Mill as part of clinical practice, some limitations of the C-Mill were also
identified, which feed back to the first translation chasm of proposing a clinical application. For example, the C-Mill’s projected environmental context imposed no constraints in height, evoking primarily step adjustments in the horizontal plane rather than in the horizontal and vertical plane as required by real-life 3D obstacles (e.g. steps, curbs, and inclines). In addition, (adaptability) treadmill walking does not allow for slowing down walking speed as occurs naturally when step adjustments are required in response to environmental context [30]. Furthermore, not all aspects of walking adaptability were addressed using the C-Mill. The C-Mill allows for visually guided target stepping, obstacle avoidance and speed-related walking adjustments, but not for turning and bending, walking around objects, walking on uneven surfaces such as stairs, ramps and grass, and walking under different ambient conditions [47]. Walking adaptability covers a broad spectrum of situations because walking adaptations may be required under various task and environmental demands [47]. The assessment and training of walking adaptability must therefore reflect this multi-faceted and complex nature of walking adaptability [47], which is only partly possible using the C-Mill.

The development of the Interactive Walkway (Technology4Science, Vrije Universiteit Amsterdam, the Netherlands) for the overground assessment of walking adaptability represents an interesting development in that regard [49, 50]. The interactive walkway uses multiple Microsoft Kinect v2 sensors for markerless 3D full-body movement registration and a projector for presenting gait-dependent visual context on the floor. This allows not only for the assessment of obstacle avoidance, target stepping assessments and speeding-up and slowing-down, but also for turning, bending, slalom, and gait initiation and termination assessments. Time series of 3D full-body kinematics and derived gait parameters obtained with a multi-Kinect v2 set-up have been shown to match well with those derived with an Optotrak motion-registration system, which is generally seen as the gold standard in terms of 3D measurement accuracy of human movement [51]. The reliability of outcome measures for various gait-environment interactions using the Interactive Walkway in both healthy adults and fall-prone older adults including patients with Parkinson’s disease and stroke is currently under study in a collaborative project within the Technology in Motion consortium (tim.lumc.nl). First results have shown that Interactive Walkway walking-adaptability outcome measures are reliable and sensitive to task and subject variations in well-functioning healthy persons [49, 50]. Moreover, the Interactive Walkway is currently deployed for the assessment of walking adaptability in the study by Timmermans et al. [46], which evaluates the
effect of walking adaptability treadmill training and an overground walking adaptability program after stroke.

C-Mill adaptability treadmill training and conventional treadmill training interventions were combined with usual physical therapy in Chapter 8. This was done amongst other reasons to practice multiple aspects of walking adaptability. However, the question is to what extent walking adaptability aspects like turning, bending, walking around objects, walking on uneven surfaces such as stairs, ramps and grass, and walking under different ambient conditions were practiced during usual physical therapy. The usual physical therapy sessions were not strictly defined and merely guided by locally implemented guidelines. Moreover, other activities that are necessary for discharge to home were also practiced during the usual physical therapy sessions. These included transfers, handling walking aids and household chores, which cannot be practiced on a treadmill. For this reason, C-Mill adaptability treadmill training may best be viewed as an integral part of an individualized rehabilitation program instead of a secluded intervention.

**Second translation chasm**

It is a challenge for the future to develop a minimal set of complementary measures for the clinical assessment of the full repertoire of walking skills required for safe everyday walking [47]. Based on the results reported in Chapter 2, the C-Mill based protocol of obstacle avoidance and visually guided stepping may form part of this comprehensive assessment of walking ability since it covers, with adequate face validity, a new construct of walking ability beyond the standard clinical walking tests. However, more research is needed to bridge the second translation chasm to a proven clinical application of the C-Mill in the assessment of walking adaptability. For example, the test-retest reliability of the C-Mill based assessment of walking adaptability should be evaluated as well as its sensitivity to change after clinical interventions. In addition, the generalizability of the results to daily living should be assessed. Chapter 2 revealed no significant differences in walking adaptability scores between subgroups stratified by fall history or fear of falling. However, the incidence of falls is determined by the combination of walking adaptability and exposure to challenging and risky situations. Future research should therefore determine the relation between the walking adaptability scores and, for example, measures of daily physical activity and participation. The relation with fall incidence should also be evaluated further, preferably prospectively.

The fact that there is currently no comprehensive clinical assessment of walking adaptability hampers the evaluation of the efficacy of interventions aimed
at improving walking adaptability [47]. One of the strengths of the work reported in the present thesis is that both clinical and laboratory outcome measures were used in evaluating the efficacy of adaptability treadmill training. Chapter 5 included a challenging and time-constrained laboratory obstacle avoidance task and revealed promising improvements in obstacle avoidance performance after only ten 1-hour sessions of adaptability treadmill training. In fact, the laboratory tasks on obstacle avoidance and related attentional demands showed the largest relative improvements (i.e., compared to the standard clinical gait and balance tests). However, unlike the study described in Chapter 8, this study did neither include a control group nor multiple follow-up measurements. Chapter 8, on the other hand, included clinical tests only, which showed no noticeable differences between adaptability treadmill training, conventional treadmill training and usual physical therapy. The outcome measures used in Chapter 8, including an overground timed obstacle avoidance task, may have covered the construct of walking adaptability insufficiently. As shown in Chapter 2, the unique aspect of walking adaptability as an important aspect of walking ability is probably related to the ability to make step adjustments under time pressure, which was not evaluated in Chapter 8.

To make a step forward in the second translation chasm (Figure 9.1 and Table 9.1), future research should combine the merits of both studies and entail randomized controlled trials with multiple follow-up measurements that comprise a challenging and comprehensive assessment of walking adaptability as outcome measure. As described above, the study by Timmermans et al. [46] is an example of such a study, comparing adaptability treadmill training with an overground walking adaptability program and exploiting the merits of the Interactive Walkway for the assessment of walking adaptability. Furthermore, it is important to evaluate whether adaptability treadmill training results in improvements outside the clinic or laboratory (i.e., in everyday life). Chapter 8 revealed clinically relevant reductions in fall rate and the proportion of fallers after adaptability and conventional treadmill training relative to usual physical therapy (37%-49% reduction). However, these reductions did not reach significance, presumably due to the limited sample size. Future studies should therefore include large(r) sample sizes to examine the clinical potential of adaptability treadmill training for reducing falls but also for increasing physical activity and participation. Such studies should entail sufficient contrast between interventions, in order to be able to detect intervention effects differentially.
Third translation chasm
When we have bridged the second translation chasm and achieved a proven clinical application of the C-Mill, the third translation chasm can follow. Translation activities in this chasm focus on implementing and adopting the proven clinical application in clinical practice [1] (Figure 9.1 and Table 9.1). Implementation seems to be most successful when the environment or setting in which the clinical application is to be implemented is receptive to change, when there is appropriate facilitation of the change, and when evidence for the clinical application is high [40]. Evidence is defined in this context as the combination of research, clinical expertise and patient choice [40]. After all, if clinicians and patients reject an intervention with demonstrated effectiveness, then it is unlikely to be widely adopted [40]. Conversely, if clinical experience and patient preferences are in favor of an intervention even though the research evidence is low, it may still be adopted and implemented [40]. The rapid increase in the number of C-Mill’s in rehabilitation centers is interesting in that regard. Despite the absence of firm evidence for its clinical application (i.e., the C-Mill has not yet progressed to a proven clinical application in the translation continuum, Figure 9.1 and Table 9.1), there are currently nearly 100 C-Mill’s installed by ForceLink and Motekforce Link in more than 15 countries across the world. In contrast, when we started the research presented in this thesis (in 2010) there were only two rehabilitation centers with a C-Mill (Reade, Amsterdam, the Netherlands and Heliomare, Wijk aan Zee, the Netherlands). The question that arises is whether it is necessary to achieve a proven clinical application before the proposed application can be adopted and implemented in clinical practice. It takes a long time to translate research findings to practice; durations of 17 to 54 years have been reported [52, 53]. In the case of the C-Mill, it seems that practice has overtaken scientific research; the C-Mill is already used worldwide while research on its usability, validity and efficacy has just begun. Notwithstanding the importance of obtaining (firm) evidence for the efficacy of interventions, the large number of C-Mills currently used for clinical and research purposes speaks to its usability and validity. In addition, it seems that the uptake of a new intervention, the C-Mill in this case, benefits from collaborations between science, clinical professionals and industry.

Although many C-Mills have been installed in a relatively short period of time, the C-Mill in clinical practice is in my experience mainly used in single training sessions rather than in progressive intervention programs or for the assessment of walking adaptability. Perhaps, we should develop evidence-based guidelines or even protocols for using the C-Mill in clinical practice. These
guidelines or protocols should specify which patients should be assessed or trained using the C-Mill, and in which way and at what time. My fellow PhD candidate Celine Timmermans is currently working on such a project, with the aim to define C-Mill adaptability treadmill training protocols supported by both objective information on performance gains from session to session as well as by subjective information on the efficacy and quality of the intervention from a user’s perspective (i.e., both patient and therapist). In other words, assessments and training of walking adaptability using the C-Mill will be linked in her project to generate adequate and personalized training protocols, thereby fully exploiting the advantage of the C-Mill as an instrument allowing for scaled manipulations of training content and content difficulty.

Alternatively, we could label the C-Mill as a therapeutic tool that can be deployed during sessions of physical therapy, just as is the case with parallel bars, wobble boards and training stairs, for which scientific evidence is also largely absent. In that way, adaptability treadmill training will be deployed mostly in single sessions, as seems currently the case in clinical practice. However, there is some indication that even single-session interventions can already result in beneficial effects with regard to fall risk [54-56]. For example, previous studies have shown that a single session of repeated-slip training in older adults has considerable benefits in reducing falls in the laboratory, even at six months after a single training session [54, 56]. Moreover, a single session of repeated-slip training has been shown to significantly reduce older adults’ risk of falls in everyday living during a 12-month follow-up period [55]. In this respect it would be interesting to examine the changes in walking adaptability that occur during a single session of adaptability treadmill training. The project of Celine Timmermans, which links the assessment and training of walking adaptability, is likely to provide useful insight in that regard. In addition, the effects of a single adaptability treadmill training session should be examined in relation to fall risk and participation.

Regardless of the approach taken, the one followed should be implemented in clinical practice. An external expert in change management should be appointed to help understand and introduce the C-Mill in clinical practice depending on the adopted approach [40]. Such an external facilitator seems to play a key role in successful implementation by stimulating and guiding change, and by training a local, internal facilitator who reinforces support on a daily basis, as is required to achieve sustained changes [40]. The implementation project described in Chapter 3 may provide a blueprint for wider implementation and adoption of assessment and training using the C-Mill, which will be bolstered further by the online platform
(http://www.move.vu.nl/nl/onderzoek/c-mill-kennisplatform/) for finding and sharing knowledge about the C-Mill [57]. Eventually, the clinical effectiveness of the C-Mill (i.e., its effect in actual clinical practice, not to be confused with efficacy as previously discussed in the section *Efficacy of adaptability treadmill training*) needs to be examined in order to achieve an established standard of care with public health impact (Figure 9.1 and Table 9.1). This would ideally imply the deployment of the C-Mill to assess and train walking adaptability, leading to improved safe everyday walking, participation and reduced fall incidence (Figure 9.1 and Table 9.1).

**Conclusion**

In this thesis, the usability, validity and efficacy of the C-Mill for the assessment and training of walking adaptability were evaluated. The work presented showed that adaptability treadmill training successfully targeted task-specific walking adjustments with great amounts of movement practice, in line with its underlying assumptions. Adaptability treadmill training further appeared usable in terms of its safety and practicability. The C-Mill was thus demonstrated to provide a usable and valid therapeutic tool for training walking adaptability. Adaptability treadmill training was shown to be effective in improving walking-ability- and walking-adaptability-related outcome measures in persons in the chronic stage after stroke and in older adults with a recent fall-related hip fracture. However, the expected surplus value of adaptability treadmill training over other forms of therapy was not demonstrated, possibly because this new construct still lacks sensitive and comprehensive walking adaptability outcome measure. Walking adaptability is a complex, multifaceted construct, which is difficult to assess in a comprehensive manner. The insights obtained in this thesis provide guidance on the road forward to a proven clinical application of the C-Mill and underscore the importance of a complementary set of walking ability measures addressing the full repertoire of skills that are necessary to walk safely in everyday life. In that sense, the studies in this thesis provide guidance to the *steps to follow toward the assessment and training of walking adaptability using the C-Mill*. 
References

Epilogue


30. Peper CE, de Dreu MJ, Roerdink M. Attuning one's steps to visual targets reduces comfortable walking speed in both young and older adults. Gait Posture. 2015; 41:830-834.


35. Bank PJM, Roerdink M, Peper CE. Comparing the efficacy of metronome beeps and stepping stones to adjust gait: steps to follow! Exp Brain Res. 2011; 209:159-169.


49. Geerse DJ, Coolen BH, Roerdink M. Walking-adaptability assessments with the Interactive Walkway: Between-systems agreement and sensitivity to task and subject variations. Revision under review