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Therapy interventions for upper limb amputees undergoing selective nerve transfers

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Corresponding Author:	A Dr. Sturma Medizinische Universitat Wien Vienna, AUSTRIA
Corresponding Author's Institution:	Medizinische Universitat Wien
Corresponding Author E-Mail:	agnes.sturma@meduniwien.ac.at
Order of Authors:	Agnes Sturma
	Laura A Hruby
	Anna Boesendorfer
	Clemens Gstoettner
	Dario Farina
	Oskar Aszmann
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TITLE:

Therapy Interventions for Upper Limb Amputees Undergoing Selective Nerve Transfers

AUTHORS AND AFFILIATIONS:

Agnes Sturma[1,2], Laura A. Hruby[1,3], Anna Boesendorfer[1], Clemens Gstoettner[1], Dario Farina[2], Oskar C. Aszmann[1,4]*

[1]Clinical Laboratory for Restoration of Extremity Function, Medical University of Vienna, Vienna, Austria
[2]Bioengineering Department, Imperial College London, London, UK
[3]Department of Orthopaedics and Trauma Surgery, Medical University of Vienna, Vienna, Austria
[4]Department of Plastic and Reconstructive Surgery, Medical University of Vienna, Vienna, Austria

Email addresses of the authors:

Agnes Sturma	(agnes.sturma@meduniwien.ac.at)
Laura A. Hruby	(laura.hruby@meduniwien.ac.at)
Anna Boesendorfer	(anna.boesendorfer@meduniwien.ac.at)
Clemens Gstoettner	(clemens.gstoettner@meduniwien.ac.at)
Dario Farina	(d.farina@imperial.ac.uk)
Oskar C. Aszmann	(oskar.aszmann@meduniwien.ac.at)

*Email addresses of the corresponding author:

Oskar C. Aszmann	(oskar.aszmann@meduniwien.ac.at)

KEYWORDS:

Rehabilitation, upper limb amputation, nerve transfer, arm prosthesis, EMG biofeedback, prosthetic training, targeted muscle reinnervation (TMR)

SUMMARY:

This work presents a protocol to enhance prosthetic function after selective nerve transfer surgery. Rehabilitation interventions include patient information and selection, support of wound healing, cortical re-activation of sensory-motor areas of the upper limb, training of selective muscle activation, prosthetic handling in daily life, and regular follow-up assessments.

ABSTRACT:

Targeted Muscle Reinnervation (TMR) improves the biological control interface for myoelectric prostheses after above-elbow amputation. Selective activation of muscle units is made possible by surgically re-routing nerves, yielding a high number of independent myoelectric control signals. However, this intervention requires the careful patient selection and specific rehabilitation therapy. Here a rehabilitation protocol is presented for high-level upper limb amputees undergoing TMR, based on an expert Delphi study. Interventions before surgery include detailed patient assessment and general measures for pain control, muscle endurance and strength, balance, and range of motion of the remaining joints. After surgery, additional therapeutic interventions focus on edema control and scar treatment and the selective activation

of cortical areas responsible for upper limb control. Following successful nerval reinnervation of target muscles, surface electromyographic (EMG) biofeedback is used to train the activation of the novel muscular units. Later on, a table-top prosthesis may provide the first experience of prosthetic control. After fitting the actual prosthesis, training includes repetitive drills without objects, object manipulation, and finally, activities of daily living. Ultimately, regular patient appointments and functional assessments allow tracking prosthetic function and enabling early interventions if malfunctioning.

INTRODUCTION:

High amputations of the upper limb provide a challenge for prosthetic replacement[1]. Aside from elbow joint function, active prosthetic systems should include opening/closing of the prosthetic hand and ideally also pronation/supination and/or wrist extension/flexion. However, the control of standard myoelectric devices usually relies on the input signals from two muscles only[2]. These are traditionally the biceps and triceps muscles after transhumeral amputations and the latissimus dorsi and pectoralis major muscles after glenohumeral amputations[3]. To control all prosthetic joints, amputees need to switch between the active joints (e.g., by using a co-contraction of the two muscles)[1]. While this provides a stable control paradigm, a significant restriction ensues with resulting slow and unintuitive control, which does not allow simultaneous movements of two or more prosthetic joints[4]. This limits the functionality of the prosthesis and is one of the reasons for high prosthetic abandonment rates after above-elbow amputations[5].

To overcome limited and unintuitive control for these types of prosthetic fittings, selective nerve transfers can be utilized. This approach, also known as Targeted Muscle Reinnervation (TMR), consists in surgically establishing myo-control signals by re-routing nerves that initially served the amputated hand and arm to different target muscles within the residual limb[6,7]. After successful reinnervation, more selective activation of the reinnervated muscle units becomes possible[8]. The resulting electromyographic (EMG) activity can then be used for prosthetic control and can yield up to six control signals.

While there is a broad agreement that TMR can significantly improve prosthetic function[9], selective activation and appropriate control of multiple muscles in the stump pose a challenge to patients, especially in the early post-operative period. This enhanced complexity of prosthetic control paired with the reduced multisensory feedback following amputation requires a specific rehabilitation to fully benefit from the surgical procedure. Here, a step-by-step guideline for the therapy interventions is provided based on recent recommendations[10]. An overview of the interventions and the estimated time they take in an ideal setting can be found in **Figure 1**.

[Place **Figure 1** here]

PROTOCOL:

The protocol was developed within a European Delphi study[10]. The assessment of its application on patients was approved by the local research ethics committee of the Medical University of Vienna and carried out according to the Declaration of Helsinki. If not mentioned otherwise, the steps described here should be carried out by an occupational therapist or a physiotherapist.

1. Pre-surgical interventions

1.1. See the patient for a multidisciplinary consultation.

NOTE: The medical core team should include a surgeon, an occupational therapist and/or physiotherapist, a prosthetist, and a psychologist.

1.2. Collect the patient history (reason and date of amputation, previous medical/therapeutic interventions after amputation, co-morbidities, general medical history, prosthetic satisfaction) and ask about expectations for prosthetic rehabilitation and demands for a prosthetic system in daily life.

1.3. Check for relevant inclusion and exclusion criteria.

1.3.1. Consider the patient for TMR if they fulfill the following criteria: amputation above the elbow, good general health, personal desire for good prosthetic function, willingness to participate in post-surgical therapy for up to 15 months.

1.3.2. Exclude patients who have any untreated psychological co-morbidities.

1.4. Perform a physical examination of the residual limb, focusing on skin and soft tissue problems, neuromas, range of motion, and possible additional nerve injuries.

NOTE: If surgical interventions for the residual limb are needed (e.g., soft tissue corrections), the surgeon addresses them during TMR surgery.

1.5. Evaluate the patient's general fitness regarding whether they will be able to carry a myoelectric prosthesis after TMR (~3 kg) and determine further interventions they may need during rehabilitation (such as strengthening the limb, exercises for endurance, or trunk stability). If the patient has a prosthesis, assess its function, preferably with standardized assessment instruments.

1.6. Evaluate the patient's mental well-being and recognize psychiatric diseases, such as depression or post-traumatic stress disorder (psychologist). If the evaluation shows the need for treatment, ensure as a team that the patient receives it.

1.7. Based on the patient's wishes, patient history, and examination, discuss available prosthetic options with the patient. Ensure that the patient understands that TMR involves a lengthy rehabilitation, where active involvement is needed.

1.8. Try to understand whether TMR is the best option for the patient. Give the patient enough time to consider different options and/or discuss them with friends and family.

1.9. See the patient again (either in the full interdisciplinary team or as a rehabilitation professional with the surgeon) to plan the procedure unless the patient had already decided on TMR during the initial consultation.

1.10. If the medical team and the patient agree that TMR should be performed, ensure that financial reimbursement of the whole process is guaranteed and that rehabilitation and prosthetic fitting will be organized.

1.11. See the patient for therapy sessions before surgery. According to the patient's need, include exercises for pain treatment, endurance, body symmetry, trunk stability, strengthening of the limb and posture, and motor imagery tasks.

1.11.1. Additionally, train one-handed activities and support the patient with assistive devices, which can be helpful to support independence in activities of daily living.

NOTE: At least one pre-surgical therapy session is recommended. More may be needed to address specific problems. If only a short time before surgery is available, include particular interventions in the post-surgical therapy.

1.12. Perform the TMR surgery (surgeon)[9].

2. Early post-surgical interventions

2.1. In the first days after surgery, mobilize the patient and ensure that they regain their physical fitness. Once more, remind the patient that reinnervation might take ~ 3–6 months.

NOTE: Early post-surgical interventions should happen once or twice daily while the patient is hospitalized. If the patient can perform the below-listed interventions by themselves after initial explanations, a therapy session once a month is sufficient and can also happen as teletherapy in an online setting. Otherwise, seeing the patient twice a week for 30–60 min is recommended.

2.2. Treat possible edemas in the area of the surgery by bandaging, using custom-made liners, propping up the residual limb and/or offering lymphatic drainage. Ensure that the patient receives adequate pain medication.

2.3. Start with scar treatment (scar cream application and scar massage) when the wounds are fully closed. Improve the range of motion in the shoulder joint for transhumeral amputations by passively moving the arm and instructing the patient to perform active exercises using the full range of movement.

NOTE: The patients are asked to use the scar cream available to them; nothing specific is recommended.

2.3.1. Communicate all interventions with the surgeon and/or see the patient with the surgeon

at least once.

2.4. If the patient had a prosthetic fitting before surgery, evaluate whether it can be re-fitted. If needed, have a prosthetist change the socket or replace the electrodes in a myoelectric fitting.

NOTE: In some cases, a re-fitting of the socket might not be feasible.

2.5. Facilitate the reinnervation process on a cortical level: Use methods such as mirror therapy[11,12], imagined movements[13], or lateralization training[14] (or follow the structure of Graded Motor Imagery, which includes these interventions[15]) to activate the sensory-motor cortex areas responsible for the upper limb.

NOTE: This enables the patient to activate reinnervated muscles more efficiently at a later point in therapy.

2.5.1. For mirror therapy, set up a mirror in front of the patient and ask them to hide the residual limb behind the mirror. Instruct them to perform different movements with the healthy hand while watching its reflection in the mirror.

2.5.2. Ask the patient to imagine different movements of the amputated hand and arm while keeping their eyes closed. If helpful, ensure that the patient can do this in a quiet, undisturbed environment.

2.5.3. For lateralization training, present the patient with cards that show either left or right hands and arms. Ask the patient to name the side and give the patient feedback on their choice.

NOTE: If the patient prefers novel technologies, introduce the patient to computer programs or apps that provide the same function.

2.6. Continue any pre-surgical interventions depending on the patient's needs.

3. Signal training

3.1. Study the surgery report to understand which muscle parts are reinnervated and which nerves were transferred. Understand that the transferred nerve determines the motion(s) the patient needs to think of to activate the reinnervated muscles (e.g., any muscle innervated by the ulnar nerve can be activated by imaging hand closing or wrist flexion after successful reinnervation).

NOTE: If anything is unclear, meet the surgeon to discuss the nerve transfers and the rehabilitation plan.

3.2. Three months after surgery, start testing for the first volitional contractions of the reinnervated muscles. If an activity can be found, continue with the steps below, and aim to see

the patient for weekly or bi-weekly therapy sessions until sEMG control is mastered. If no activity can be found, continue with the early post-surgical interventions, and perform another test a few weeks later.

3.2.1. For evaluating volitional muscle activity, set up a system for surface EMG (sEMG) biofeedback.

NOTE: Here, a system that can display up to six EMG signals and allow an individual amplification of each channel is preferred.

3.2.2. Prepare the patient's skin to reduce impedance by removing excessive body hair, dead skin flakes, oil, or skin cream[16]. Explain the goal of the assessment and the functionality of the system to the patient.

NOTE: Plan therapy sessions for 30 min or less at this stage. Otherwise, muscles may become easily fatigued, and the patient may lose needed focus. If short sessions are not possible, mix different therapy interventions (EMG and posture training) to avoid fatigue. **Figure 2** displays a standard setup for EMG biofeedback training.

[Place **Figure 2** here]

3.2.3. Instruct the patient to perform hand and arm movements depending on the original function of the donor's nerves (e.g., hand closing if the ulnar nerve was used) and try to palpate the muscle.

3.2.4. Place a surface EMG electrode on the skin above the muscle. Consider reinnervation to be successful if the signal amplitude during activation is 2–3 times higher than during relaxation[17].

3.2.5. If such activation is not possible, instruct other movements connected to the donor's nerve (e.g., flexion of the wrist or pinkie finger, if the ulnar nerve is the donor) and move the electrode slightly above the recipient's muscle.

3.2.6. Repeat the evaluation for volitional activation with all nerves based on the surgery reports and note which muscles can be activated and with which motor command. Ask the patient to train the motor commands at home.

3.3. Train the selective activation of the reinnervated muscles.

3.3.1. Use EMG biofeedback to display the activity of one muscle. Ask the patient to think of the previously evaluated movement patterns and use an sEMG electrode (see **Table of Materials**) to pick up the recipient's muscle signals.

3.3.2. Use the notes from the previous evaluation. If easier for the patient, ask them to perform the desired movements bilaterally.

3.3.3. As soon as the patient can repeatably activate the muscle, train muscle relaxation as well.

NOTE: Muscle relaxation corresponds to EMG amplitudes close to zero and is sometimes hard to achieve.

3.3.4. Ask the patient to activate the muscle and fully relax it repeatedly. Make sure that there are 5–10 s of break in between the activations.

3.3.5. Instruct the patient to perform different movements and vary electrode positions to find the combination leading to the highest amplitude (hotspot). Take a photo of the best position or mark it on the skin.

3.3.6. If more muscles can already be activated, train the activation and relaxation of each muscle individually.

3.3.7. After a reasonable control of the single muscles is possible, display the activity of two muscles. Start with antagonistic muscles/movements such as hand opening and closing. Instruct the patient to activate one muscle while the other one should be as relaxed as possible.

3.3.8. Try different movement cues for both muscles if such a selective activation is not possible. Explain to the patient that selectivity needs some training and make enough time for this step.

3.3.9. As soon as the selective activation of two muscles is achieved, add a third muscle and repeat the previous step. In the same way, add one muscle at a time until the patient can selectively activate each one. Plan several therapy sessions to train this.

NOTE: To allow direct simultaneous prosthetic control at a later stage, the patient needs the ability to repeatedly activate each muscle while maintaining a deficient activation of all others. **Figure 3** shows a schematic drawing of the excellent separation of six different signals in an EMG biofeedback system.

[Place **Figure 3** here]

3.4. Once the selective activation of all signals is established, introduce a table-top prosthesis as shown in **Figure 4**.

NOTE: Some systems allow to display EMG signals while moving the prosthesis simultaneously. These systems are prefered for training as they enable more precise feedback.

[Place **Figure 4** here]

3.4.1. First, only enable one prosthetic joint, e.g., the hand, and ask the patient to control it while carefully watching the prosthesis. If the prosthetic hardware allows it, explain to the patient

that a low EMG amplitude corresponds to slow movement while fast movement is achieved through a high signal. Let them test different movement speeds.

3.4.2. Change the active prosthetic joint (e.g., elbow joint or wrist) and let the patient control these levels with their EMG signals.

3.4.3. Once a good control of the single levels is possible, switch on all prosthetic joints and enable simultaneous control. Instruct the patients that unwanted prosthetic movements are normal at this initial stage of prosthetic control.

NOTE: A light activation of their muscles may support selective control of single prosthetic joints.

3.4.4. When this is mastered, give the patient a first impression of grasping with a prosthetic device (the table-top prosthesis) by holding objects (small balls, tubes of bottles) close to the open prosthetic hand and asking them to close.

3.4.5. If they want, let the patient play with grasping and releasing objects they hold with their unaffected hand (for unilateral amputations). Let the patient know that sometimes failing to grasp or release objects is normal but should improve with training.

3.5. Ensure that a certified prosthetist provides a test-fitting with all electrodes for myoelectric control placed in the socket correctly.

3.5.1. To support the correct electrode placement in the socket, mark the EMG hotspots on the patient's skin and note the prosthetic movements for each hotspot.

3.5.2. If possible, see the patient with the prosthetist for the plaster casting and answer any questions the prosthetist might have regarding electrode placement.

3.5.3. When the first (test-) socket is ready, check its fit together with the prosthetist. Ask the patient to wear it and report any issues with the fitting (such as too much pressure at specific points). Check the electrode positions by connecting the electrodes in the socket to an EMG biofeedback system or a table-top prosthesis and asking the patient to control it.

3.5.4. If no sufficient control of the table-top prosthesis is possible when wearing the socket while it can be done with electrodes mounted on the skin, re-assess the electrode positions in the socket with the prosthetist and change them (and/or the socket) if needed.

4. Prosthetic training

4.1. Once the (test-)socket fits well and the patient can control a table-top prosthesis with the electrodes embedded in the socket, ask the prosthetist to assemble the complete prosthetic fitting.

4.2. See the patient with their new prosthetic fitting together with the prosthetist and surgeon. Check the fit of the prosthesis, discuss with the team whether the changes are needed, and answer any questions the patient might have.

4.2.1. Explain the basic functionality of the prosthesis to the patient, such as degrees of freedom, how switching between the active joints works (if needed). Also, explain whether the prosthesis is waterproof and how it should be cleaned.

4.3. Train donning and doffing of the prosthesis.

NOTE: The duration and frequency of prosthetic training depends on the complexity of the prosthetic fitting, the therapist's experience, and the patient's motor learning ability. Needed changes in the socket (e.g., for electrode positions) may delay the training. In optimal settings, the patient attends therapy twice a week for 30–60 min in the first few weeks and has the option of using the test fitting for home training in between.

4.4. Train prosthetic movements without external objects.

4.4.1. Ask the patient to perform easy movements of the prosthesis, such as opening/closing of the hand. If possible, connect the prosthesis *via* Bluetooth to its software to display EMG signals.

NOTE: If the prosthesis does not react to the patient's motor commands or perform unintended movements, use the EMG biofeedback to figure out the reason for this. If the problem is hardware-related (socket-fit or electrode placement), contact the prosthetist to solve this. Otherwise, try adapting the software settings and/or instruct the patient to adjust the motor commands (e.g., slighter contraction).

4.4.2. Continue with training single movements of all prosthetic joints as described in step 3. If the prosthesis allows different movement speeds, instruct the patient to vary the speed of movement. Ensure that the patient is precisely doing what they intend to do.

4.4.3. To add more complexity, ask the patient to control the prosthesis in different positions (standing, sitting, or with varying shoulder positions for transhumeral amputees) and combine more degrees of freedom simultaneously (e.g., closing the hand flexing the elbow at the same time).

4.5. Train object manipulation

4.5.1. Provide the patient with different objects such as stress balls or wooden blocks. Explain that the manipulation of objects adds another layer of complexity.

NOTE: Normally, the patient needs to train for a while to have complete control over the prosthesis while working with external objects.

4.5.2. Ask the patient to use their healthy hand (for unilateral amputees) to put the object into the prosthetic hand. Then, close the prosthetic hand, move the prosthetic elbow and/or wrist joint, and, finally, release the object.

4.5.3. As a next step, place the objects on the table/shelf/etc. Ask the patient to pick them up with the prosthetic hand and place them somewhere else.

4.5.4. Finally, tasks that require more precision, such as stacking wooden blocks or grasping a ball rolling on a table, can be trained.

4.6. Train activities of daily living

4.6.1. Ask the patient which common activities (such as carrying a bag, doing the laundry, cooking, dressing, eating with cutlery, opening/closing a door, etc.) they regularly do in their daily life. Prioritize a few of them and train them in therapy.

NOTE: Discuss that for bathing and showering, the prosthesis cannot be used.

4.6.2. For training daily activities, suggest performing them with the prosthesis based on the experience (e.g., with some prosthetic hands, it is easier to pick up small objects if the hand is in a maximum pronated position). Let the patient perform the tasks based on suggestions provided. If they have other ideas on how to perform them, let the patient try their approach and encourage them to try many strategies and be creative.

NOTE: It is essential to explain to patients that prosthesis training takes time and patience.

4.6.3. Give the patient feedback on the performance during task completion. The feedback should be based on compensatory movements (little to none is preferred) and the patient's time to perform the task. If you or the patient are dissatisfied with how the task could be completed, try different strategies.

4.6.4. Ask the patient which further, more specific activities are essential in their daily lives (e.g., sports, leisure activities, childcare or specific tasks required for their jobs) and discuss how they can use the prosthesis within these tasks.

NOTE: If possible, directly train a few of these tasks with the patient during the therapy sessions (either in the clinic or at the patient's home environment). Not all tasks can be performed with a prosthesis. In some cases, specific prosthetic fittings or assistive devices are needed (e.g., for some sports or playing instruments). Although there were significant advances in recent years, prosthetic devices are still far from equivalent to human hands in function[18].

4.6.5. Ask the patient to use the prosthesis at home and make notes (or photos and videos) of tasks they are doing or they feel they cannot do.

4.6.6. Use these notes to discuss different strategies for prosthetic use in the following therapy sessions.

4.6.7. Repeat prosthetic training within the therapy sessions and at home until the therapist and the patient understand that the prosthesis can be used well in daily life.

4.6.8. Discharge the patient from therapy.

5. Follow-up assessments

5.1. Invite the patient to a multidisciplinary medical consultation at 3 months after discharge from rehabilitation.

5.1.1. Ask the patient how they use their prosthesis at home and work and discuss any problems.

5.1.2. If the patient reports any problems, discuss/provide solutions for them.

5.2. Assess the patient's prosthetic function by using standardized tests (such as the Southampton Hand Assessment Procedure (SHAP)[19], the Action Research Arm Test (ARAT)[20,21], or the Assessment of Capacity for Myoelectric Control (ACMC)[22,23]). Ask the patient to fill out standardized questionnaires for quality of life and hand use in daily life (such as Short Form 36 (SF-36)[24] and Disabilities of Arm, Shoulder and Hand (DASH)[25]).

5.3. If the test results show a problem, discuss this with the patient and offer solutions for their problems (if possible).

5.4. After the first follow-up consultation, invite the patient every 6 months to a multidisciplinary consultation and structured assessments to ensure ongoing good prosthetic function.

REPRESENTATIVE RESULTS:

The described rehabilitation protocol was implemented in a clinical setting at the Medical University of Vienna, and its feasibility and outcomes were assessed in a clinical study, which was recently published[9]. As reported[9], 30 patients participated in the trial to evaluate the feasibility of TMR surgery and subsequent rehabilitation. **Figure 5** displays that out of these 30 patients, 11 underwent TMR as a pain treatment rather than a means to improve function *via* prosthetic fitting. Out of the remaining 19 patients originally aiming for a prosthetic fitting, five decided against it due to the high costs of the fitting (estimated between 75,000–150,000 €), insufficient time for rehabilitation, or high weight of the prosthesis. In one patient, intra-operative exploration revealed a global brachial plexus injury, making further nerve transfers impossible. This patient kept using his body-powered device. Of the remaining 13 patients undergoing prosthetic rehabilitation, 10 were available for a follow-up assessment.

[Place **Figure 5** here]

Outcomes were assessed using the Southampton Hand Assessment Procedure (SHAP)[19], the Action Research Arm Test (ARAT)[20,21], and the Clothespin-Relocation Test (CPRT)[6,26]. These assessments are commonly used tests to evaluate prosthetic function. The evaluation took place at least 6 months after the final prosthetic fitting. Additionally, patients were asked about their prosthetic wearing habits.

As described by Salminger et al.[9], assessment of the 10 patients after TMR surgery revealed a SHAP score of 40.5 ± 8.1 (with a healthy upper extremity having a score of about 100) and ARAT score of 20.4 ± 1.9 (with 57 being the maximum score and 0 representing no upper extremity function) (**Table 1**). In the CPRT, patients were able to complete the tasks within 34.3 ± 14.4 s. They reported wearing their prosthesis daily with a wearing time ranging from 3–10 hours per day.

FIGURE AND TABLE LEGENDS:

Figure 1: Overview of stages within the rehabilitation process, including the milestones that mark the start of a new stage.

Figure 2: Setup for surface EMG biofeedback. The therapist places an electrode on the patient's skin where the EMG signal is expected while explaining the needed movement cue (making a fist). The patient and therapist can see the patient's muscular activity (EMG) on the computer screen and use this feedback for finding the best electrode position and movement cue.

Figure 3: Schematic drawing of the EMG signals displayed *via* biofeedback. Every channel (with a different color) is mapped to a specific muscle part and will later be responsible for a particular prosthetic movement. Good separation, as depicted here, ensures that the prosthesis only makes indented movements.

Figure 4: Patient controlling a table-top prosthesis with surface electrodes mounted on his residual limb.

Figure 5: Flowchart showing the patients included in the feasibility study.

Table 1: Prosthetic function of patients following TMR surgery and rehabilitation. In the SHAP and ARAT, higher scores mean a better function, which is also indicated by less time needed in the CPRT. Total patient assessed: n = 10. Adapted with permission from Reference[9].

DISCUSSION:

In recent years, selective nerve transfers have been increasingly used to enhance prosthetic function[27]. Experienced clinicians in this field have come to appreciate that rehabilitation is essential to enable amputees to use a prosthesis after the surgical procedure skilfully[27]. However, there is a lack of structured therapy programs. The current protocol aimed to provide the

occupational and physical therapists with the tools and structure to guide the patients throughout the long TMR process. In contrast to previous suggestions for therapy (developed for less complex nerve transfers)[28], there is a stronger focus on pre-prosthetic training and the use of EMG biofeedback to allow selective muscular control.

As shown in the feasibility study[9], discussing the patient's expectations is essential for post-operative success. The inclusion of highly motivated patients certainly helped to achieve the described excellent outcomes. Less compliance to the described protocol might result in reduced prosthetic function. Additionally, not all patients wish to receive a prosthetic fitting (or can afford to get one). However, TMR may still be feasible to improve neuroma or phantom limb pain since recent studies have shown the potential of nerve transfers to alleviate these conditions[29–31]. For such cases, the rehabilitation program is foreshortened. Still, we have experienced that regular training of controlled activation of the reinnervated muscles and a prosthesis can further improve the pain situation[32]. Here, shared decision-making is essential as some patients might wear a prosthesis for its potential to reduce pain in the long term[32], while others might not be interested.

In our experience, a detailed discussion with the patient is essential to evaluate future compliance. Depending on the reinnervation time, motor learning capacity, and the patient's availability, the rehabilitation process is likely to take between 9–15 months. Suppose a patient does not strive toward the improvement of upper limb function or might make better use of another device (e.g., body-powered prosthetics). In that case, one might not consider the time (and possibly financial) commitment worth it. To save resources, we strongly recommend only including patients who express a strong interest in the procedure and only perform the surgery for functional purposes when the full rehabilitation procedure is anticipated. Finally, the costs for the surgery, therapy, and fitting should likely be covered at that point.

The described study protocol needs to be adapted for each individual based on clinical reasoning to meet their specific needs. Physical and psychological co-morbidities need to be considered and adequate treatment (e.g., psychotherapy) offered in addition to the interventions described here. In patients receiving TMR immediately after amputation, a closer screening for psychological conditions developing overtime may be needed. Apart from this, no change in the protocol is required for this group of patients. They might even progress faster in motor learning as they might still be used to bimanual activities. Within this protocol, the nerve transfers operated by the surgeon define, which motor commands need to be trained and are expected for which muscle parts. The choice of the prosthetic end device influences prosthetic training. For multi-articulated prostheses, switching between different grasp types and how to use them needs to be included in therapy, if necessary.

For patients living far away from the clinical center or those who cannot attend in-person rehabilitation regularly, adoptions in the rehabilitation protocol are needed. They include a stronger focus on home training, the possible involvement of a therapist near the patient's home, and telerehabilitation sessions *via* online video calls. Solutions for telerehabilitation need to provide a stable video and audio connection while fulfilling all data protection requirements. In these patients, a first visit to the clinical center should be planned at 6–9 months after surgery

for signal training. The visit is usually for 1 week, with therapy sessions twice a day. In a majority of cases, good signal separation can be achieved at this time. Otherwise, another stay for signal training is needed, and the patient may get a simple sEMG biofeedback device for home training. When good signal separation is established, the prosthetist can fabricate a test socket, and the signal positions can be defined during the stay. This allows the prosthetist to create the final fitting when the patient returns home. The final prosthesis can be fitted in a second 1-week visit 1–2 months later, and prosthetic training can be initiated. Advanced prosthetic training and further follow-up visits can either happen in a remote setting or a further visit to the center, depending on the patient's needs.

Furthermore, other surgical interventions, such as osseointegration[33] to improve the mechanical interface for the prosthesis, can be combined with TMR[34]. If this is the case, specific interventions must be included (such as the graded weight-bearing training after osseointegration[35]). Additionally, while the described protocol is intended for direct prosthetic control systems (where one electrode corresponds to one movement), its principles remain the same if a pattern recognition control system is planned. The main difference in rehabilitation is that the selective activation of single muscles becomes less relevant, while particular and repeatable activation patterns of several muscles need to be trained[36].

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DISCLOSURES:

The authors do not have any conflicts of interest.

REFERENCES:

1. Vujaklija, I., Farina, D., Aszmann O. C. New developments in prosthetic arm systems. *Orthopedic Research and Reviews*. **8**, 31–39 (2016).
2. Zhou P. et al. Decoding a new neural machine interface for control of artificial limbs. *Journal of Neurophysiology*. **98** (5), 2974–2982 (2007).
3. Sturma A, Salminger S, Aszmann O. Proximale Amputationen des Armes: Technische, chirurgische und handtherapeutische Möglichkeiten. *Zeitschrift für Handtherapie*. **21** (1), 18–25 (2018).
4. Uellendahl, J. E. Upper extremity myoelectric prosthetics. *Physical Medicine & Rehabilitation Clinics of North America*. **11** (3), 639–652 (2000).
5. Biddiss E, Chau T. Upper-limb prosthetics: critical factors in device abandonment. *American Journal of Physical Medicine & Rehabilitation*. **86** (12), 977–987 (2007).
6. Kuiken, T. A., Dumanian, G. A., Lipschutz, R. D., Miller, L. A., Stubblefield, K. A. The use of targeted muscle reinnervation for improved myoelectric prosthesis control in a bilateral shoulder disarticulation amputee. *Prosthetics and Orthotics International*. **28** (3), 245–253 (2004).
7. Aszmann, O. C., Dietl, H., Frey, M. Selective nerve transfers to improve the control of myoelectrical arm prostheses. *Handchirurgie, Mikrochirurgie, plastische Chirurgie*. **40** (1), 60–65

2008.
8. Cheesborough, J. E., Smith, L. H., Kuiken, T. A., Dumanian, G. A. Targeted muscle reinnervation and advanced prosthetic arms. *Seminars in Plastic Surgery*. **29** (1), 62–72 (2015).
9. Salminger, S. et al. Outcomes, challenges and pitfalls after targeted muscle reinnervation in high level amputees. Is it worth the effort? *Plastic and Reconstructive Surgery*. **144** (6), 1037e–1043e (2019).
10. Sturma, A. et al. Rehabilitation of high upper limb amputees after Targeted Muscle Reinnervation. *Journal of Hand Therapy: Official Journal of the American Society of Hand Therapists.* In press (2020).
11. Ramachandran, V. S., Rogers-Ramachandran, D. Synaesthesia in phantom limbs induced with mirrors. *Proceedings Biological Sciences*. **263** (1369), 377–386 (1996).
12. Rothgangel, A. S., Braun, S. M., Beurskens, A. J., Seitz, R. J., Wade, D. T. The clinical aspects of mirror therapy in rehabilitation. *International Journal of Rehabilitation Research*. **34** (1), 1–13 (2011).
13. Dickstein, R., Deutsch, J. E. Motor imagery in physical therapist practice. *Physical Therapy*. **87** (7), 942–953 (2007).
14. Bowering, K. J. et al. The effects of graded motor imagery and its components on chronic pain: A systematic review and meta-analysis. *The Journal of Pain*. **14** (1), 3–13 (2013).
15. Moseley, G. L. *The graded motor imagery handbook.* Noigroup Publications. 2012.
16. Merletti, R., Parker, P. Electromyography: Physiology, engineering, and non-invasive applications. *Wiley IEEE-Press Verlag.* 2004.
17. Sturma, A., Hruby, L. A., Prahm, C., Mayer, J. A., Aszmann, O. C. Rehabilitation of upper extremity nerve injuries using surface EMG biofeedback: Protocols for clinical application. *Frontiers in Neuroscience*. **12** (906) (2018).
18. Farina D, Aszmann O. Bionic limbs: clinical reality and academic promises. *Science Translational Medicine*. **6** (257), 212 (2014).
19. Kyberd, P. et al. Practice evaluation. Case studies to demonstrate the range of applications of the Southampton Hand Assessment Procedure. *British Journal of Occupational Therapy*. **72** (5), 212–218 (2009).
20. Lyle, R. C. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Internationale Journal of Rehabilitation Research*. **4**, 483–492 (1981).
21. Yozbatiran, N., Der-Yeghiaian, L., Cramer, S. C. A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair*. **22** (1), 78–90 (2008).
22. Hermansson LM FA, Bernspang B, Eliasson AC. Assessment of capacity for myoelectric control: a new Rasch-built measure of prosthetic hand control. *Journal of rehabilitation medicine.* **37** (3), 166–171 (2005).
23. Hermansson, L. M., Fisher, A. G., Bernspång, B., Eliasson, A.-C. Intra- and inter-rater reliability of the assessment of capacity for myoelectric control. *Journal of Rehabilitation Medicine*. **38** (2), 118–123 (2006).
24. McHorney, C. A., Ware Jr., J. E., Raczek, A. E. The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical Care*. **31**, 247–263 (1993).
25. Gummesson, C., Atroshi, I., Ekdahl, C. The disabilities of the arm, shoulder and hand

(DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. *BMC Musculoskeletal Disorders*. **4** (1), 11 (2003).
26. Stubblefield, K. A. Occupational therapy outcomes with targeted hyper-reinnervation nerve transfer surgery: Two case studies. *MEC '05 Intergrating Prosthetics and Medicine, Proceedings of the 2005 MyoElectric Controls/Powered Prosthetics* (2005).
27. Geary, M., Gaston, R. G., Loeffler, B. Surgical and technological advances in the management of upper limb amputees. *The Bone & Joint Journal.* **103-b** (3), 430–439 (2021).
28. Stubblefield, K. A., Miller, L. A., Lipschutz, R. D., Kuiken, T. A. Occupational therapy protocol for amputees with targeted muscle reinnervation. *Journal of Rehabilitation Research & Development*. **46** (4), 481–488 (2009).
29. Dumanian, G. A. et al. Targeted muscle reinnervation treats neuroma and phantom pain in major limb amputees: A randomized clinical trial. *Annals of Surgery*. **270** (2), 238–246 (2018).
30. Pet, M. A., Ko, J. H., Friedly, J. L., Mourad, P. D., Smith, D. G. Does targeted nerve implantation reduce neuroma pain in amputees? *Clinical Orthopaedics and Related Research*. **472** (10), 2991–3001 (2014).
31. Souza, J. M. et al. Targeted muscle reinnervation: a novel approach to postamputation neuroma pain. *Clinical Orthopaedics and Related Research*. **472** (10), 2984–2990 (2014).
32. Sturma, A., Hruby, L. A., Vujaklija, I., Østlie, K., Farina, D. Treatment strategies for phantom limb pain. In: Aszmann, O. C., Farina, D., eds. *Bionic Limb Reconstruction*. 1 ed: Springer International Publishing. 113–124 (2021).
33. Li, Y., Branemark, R. Osseointegrated prostheses for rehabilitation following amputation : The pioneering Swedish model. *Der Unfallchirurg*. **120** (4), 285–292 (2017).
34. Vincitorio, F. et al. Targeted muscle reinnervation and osseointegration for pain relief and prosthetic arm control in a woman with bilateral proximal upper limb amputation. *World Neurosurgery*. **143**, 365–373 (2020).
35. Jonsson, S., Caine-Winterberger, K., Branemark, R. Osseointegration amputation prostheses on the upper limbs: methods, prosthetics and rehabilitation. *Prosthetics and Orthotics International*. **35** (2), 190–200 (2011).
36. Stubblefield, K., Kuiken, T. Occupational therapy for the targeted muscle reinnervation patient. In: Kuiken, T., Schultz-Feuser, A., Barlow, A. ed. *Targeted Muscle Reinnervation*. Boca Raton: Taylor & Francis Group. 99–119 (2014).

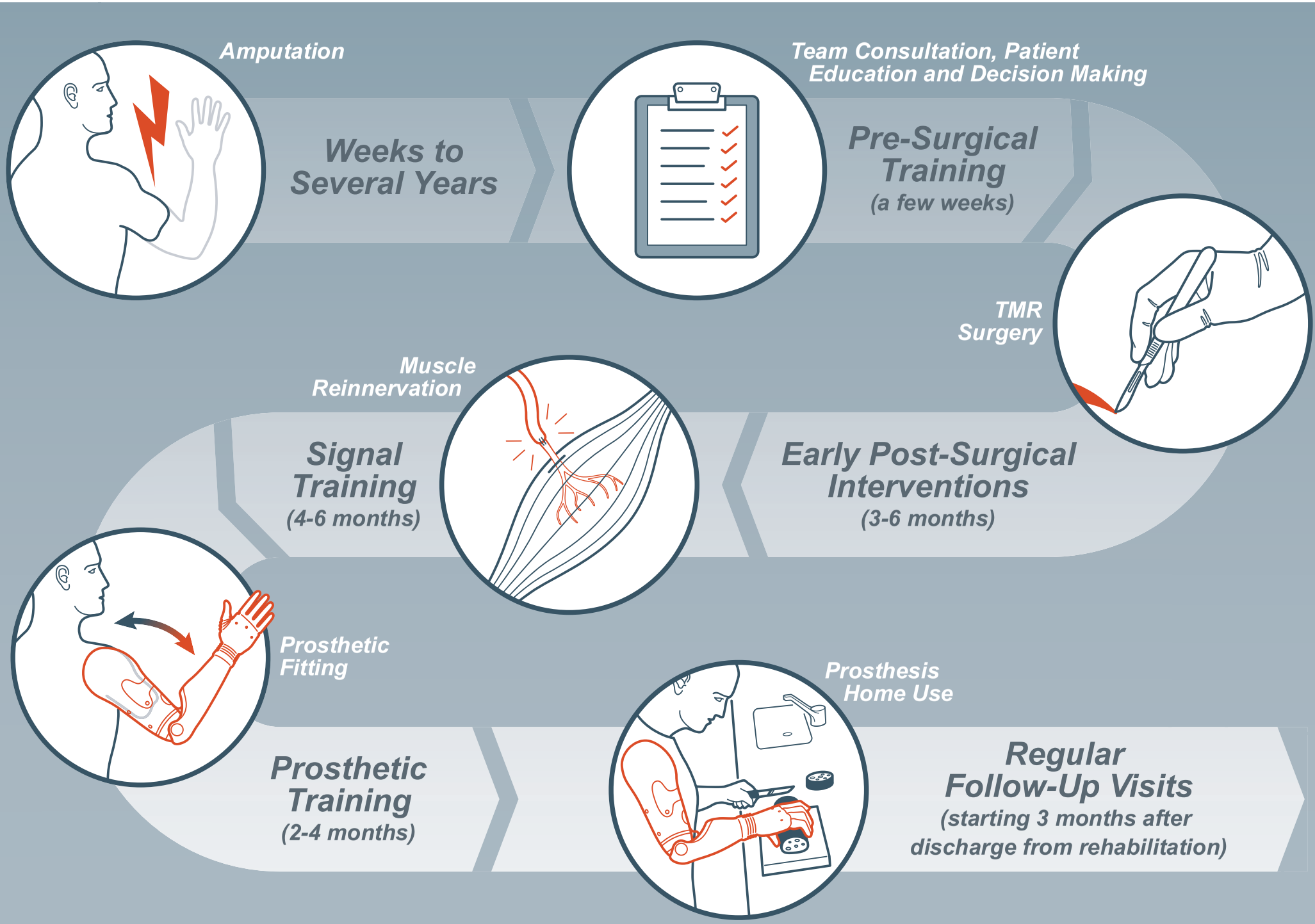

Figure 1

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Figure 2

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Figure 3

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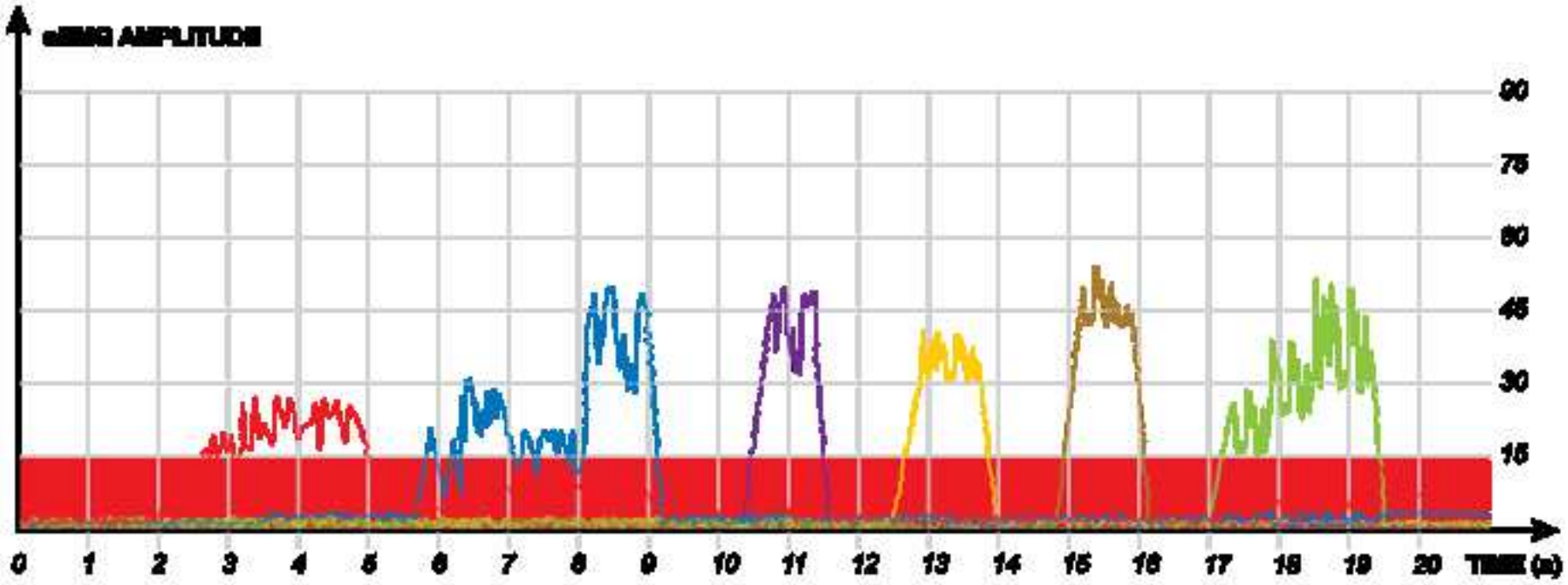

Figure 4

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Figure 5

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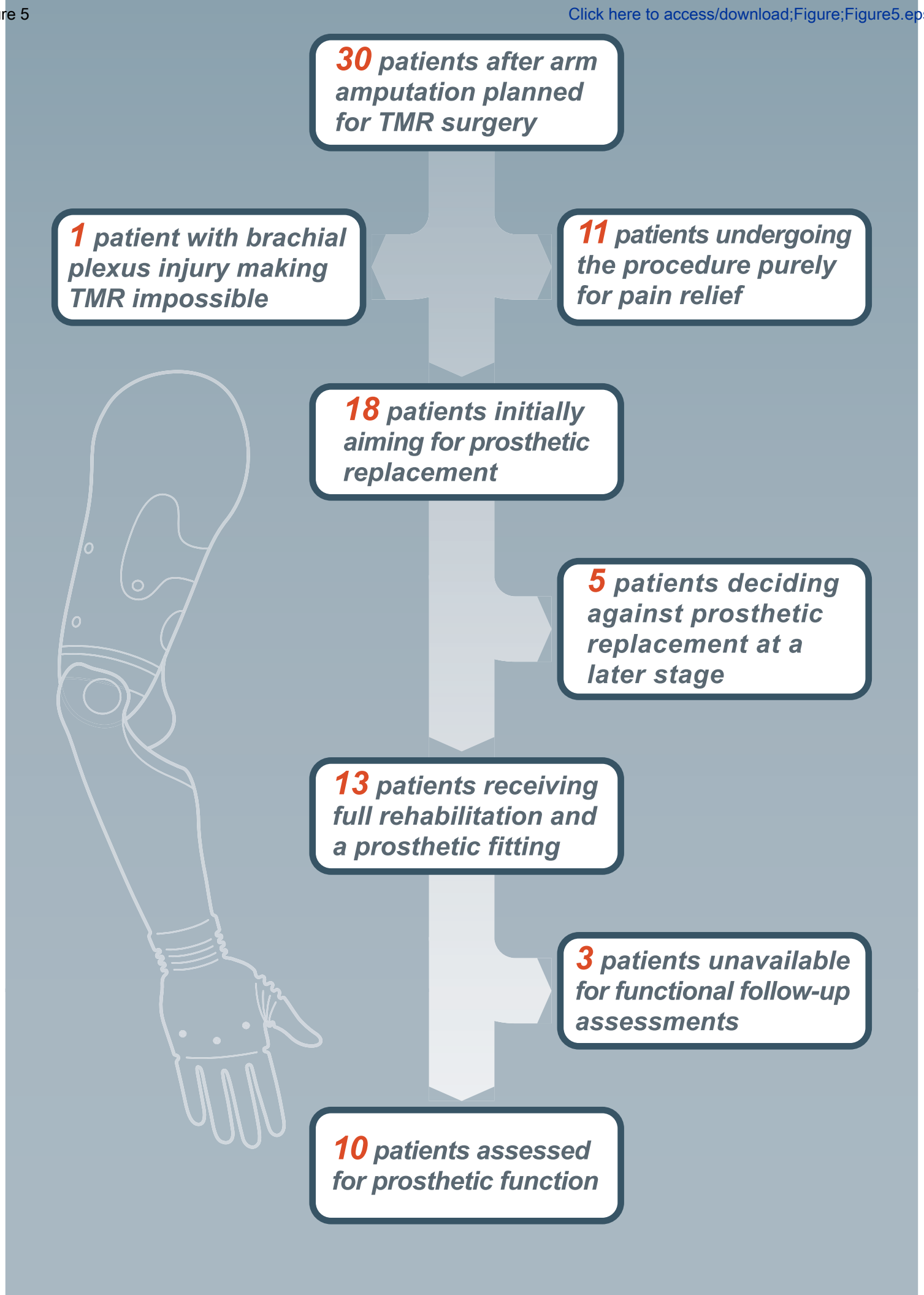

Table 1

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Outcome assesment	Score	Expected score for healthy upper extremity
SHAP	40.5 ± 8.1	100
ARAT	20.4 ± 1.9	57
CPRT	34.3 ± 14.4 s	-

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Point-to-point reply to the comments raised by reviewers and editor

Editorial comments:

Changes to be made by the Author(s):

1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.

Done.

2. Please revise the following lines to avoid previously published work: 143-144, 163-165, 168-170, 176-177, 185-186.

Thank you for making us aware of this. We have revised these lines.

3. Corresponding authors are different in the main manuscript (Oskar C. Aszmann) and the Editorial software (A Sturma, where the authors give input while uploading the manuscript). Please clarify.

While all authors were involved in the preparation and revision of the submitted manuscript, we perceived it as the easiest option, if the first author (A Sturma) took the responsibility for the organisation of the revision and submission process. OC Aszmann, however, is the senior author of the manuscript, who supervised the work, secured the funding, and was deemed the best candidate to answer reader's questions upon publication. Therefore, we chose to name A Sturma as the corresponding author in the editorial software and OC Aszmann as the corresponding author in the main manuscript. Should this not be possible, we are happy to change the correspondence so that OC Aszmann also has this role in the editorial software.

4. Please rephrase the Summary to clearly describe the protocol and its applications in complete sentences between 10-50 words: "Here, we present a protocol to …"

Done.

5. JoVE cannot publish manuscripts containing commercial language. This includes trademark symbols (™), registered symbols (®), and company names before an instrument or reagent. Please remove all commercial language from your manuscript and use generic terms instead. All commercial products should be sufficiently referenced in the Table of Materials. Please sort the Materials Table alphabetically by the name of the material.

Done.

6. Please support the statements in the introduction (paragraphs 1, 2 and 3) with more published references.

Thank you for making us aware that we had indeed a limited number of references, which we have changed in the revised manuscript.

7. The Protocol should be made up almost entirely of discrete steps without large paragraphs of text between sections. Please simplify the Protocol so that individual steps contain only 2-3 actions per step and a maximum of 4 sentences per step.

We have revised the protocol accordingly.

8. Please ensure that all text in the protocol section is written in the imperative tense as if telling someone how to do the technique (e.g., “Do this,” “Ensure that,” etc.). The actions should be described in the imperative tense in complete sentences wherever possible. Avoid usage of phrases such as “could be,” “should be,” and “would be” throughout the Protocol. Any text that cannot be written in the imperative tense may be added as a “Note.” However, notes should be concise and used sparingly. Please include all safety procedures and use of hoods, etc.

We have revised the protocol and made sure that most of the protocol is written in imperative tense.

9. Please note that your protocol will be used to generate the script for the video and must contain everything that you would like shown in the video. Please ensure you answer the “how” question, i.e., how is the step performed? Alternatively, add references to published material specifying how to perform the protocol action. There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol.

We feel that this should be the case in the revised manuscript.

10. Please add more details to your protocol steps.
Step 1.1: Please include any patient inclusion/exclusion criteria.

We have added a new step 1.2 in which we explicitly mention the inclusion and exclusion criteria.

Step 2.2: Please provide details about how the processes of pain control, scar treatment are performed.

Done.

Step 2.4: Please note that to film this step, we need more explicit details. The citation of the references cannot be filmed.

We have added sub steps.

Step 3.2.1: “Prepare patient’s skin to reduce impedance,” how is this done?

We have added this information.

Step 3.3.2: Please specify the break period.

Done.

11. Line 334: Please mention the approximate cost to be born by the patients.

While we are aware that there is a high variance of costs depending on geographical location and type of prosthesis, we have added approximate costs we would expect for a fitting (between 75 000€-150 000€).

12. Please include a one-line space between each protocol step and then highlight up to 3 pages of the Protocol (including headings and spacing) that identifies the essential steps of the protocol for the video, i.e., the steps that should be visualized to tell the most cohesive story of the Protocol. Remember that non-highlighted Protocol steps will remain in the manuscript, and therefore will still be available to the reader.

Done.

13. As we are a methods journal, please revise the Discussion to explicitly cover the following in detail in 3-6 paragraphs with citations:
a) Critical steps within the protocol
b) Any modifications and troubleshooting of the technique
c) Any limitations of the technique
d) The significance with respect to existing methods
e) Any future applications of the technique

The revised discussion should meet these criteria.

14. Figure 3: Please provide the x and y-axis description. Also, please ensure that the x-axis values distinctly visible.

We have changed figure 3 so that it is now a schematic drawing, including an axis description and distinct values (seconds) for the x-axis.

15. Please revise the table of the essential supplies, reagents, and equipment. The table should include the name, company, and catalogue number of all relevant materials in separate columns in an xls/xlsx file. Please sort the Materials Table alphabetically by the name of the material.

Done.

16. Please spell out the journal titles in the References.
Done.

_____

Reviewers' comments:

Reviewer #1:

Manuscript Summary:
This is a step-by-step guideline /protocol for therapeutic interventions and rehabilitation for proximal upper extremity amputees after TMR surgery aimed at improved prosthetic control. In this relatively young field, such a protocol has been lacking in the literature, and it will indeed be useful for multidisciplinary groups dealing with this patient group in general, and for the therapists of these group in particular.

The paper is well written, concise, and includes the necessary introductory as well as conclusory sections. The protocol is based on a Delphi study as well as the vast experience of the Vienna group in this field, and as such is well founded and will surely be accepted and welcomed by groups all over the world.

Thank you for taking the time to review our manuscript and thank you for you encouraging feedback.

Major Concerns:
No major concerns.

Minor Concerns:
There are some minor concerns. Some clarifications and further recommendations are left with the reader after taking part of this manuscript.

1) In several instances the protocol is lacking in recommendations of frequency and/or timing of interventions. While everyone working in this field realizes that there are no absolutes, the less experienced group would surely benefit from the recommendations of the authors' group.
a) is there a minimum time before surgery that pre-surgical multidisciplinary consultation should take place in order to permit enough time for preoperative interventions?
b) is one multidisciplinary session enough? If the patient is to be given enough time to consider different options, are more than one visit required?
c) regarding therapy sessions before surgery: is there a recommendation on frequency and/or number of sessions? If not, how many visits are required on average?
d) in the early post-operative period, does the therapist meet the patient every day? Again, frequency and timing of sessions is of interest to the reader.
e) in section 3 (Signal training), there is a recommendation on when to start (3mo) and when to try again if reinnervation cannot yet be confirmed (a few weeks later). This is very helpful, and more such recommendations are needed both regarding the continuation of post-surgical interventions, possible visits after post-surgical interventions are finished but before signal training is initiated, and especially regarding the frequency of therapy session during the Signal training phase.
f) the same concern applies to section 4 (Prosthetic training). A recommendation on frequency of sessions and expected length of each stage is sorely needed.
g) based on the above concerns, I humbly suggest that some ideal, or expected averages should be

given for the frequency of sessions and duration of each stage. I further suggest that figure1 would be changed to include these recommendations.

Thank you giving us such structured feedback on missing information regarding the timing and frequency of rehabilitation. We agree that details on timing and intensity are very relevant information. We have added recommendations for rehabilitation frequencies, and expected time frames in the revised manuscript. Also, we have added the time frames in figure 1. Along with this information, we inform the reader that these should be seen as optimal scenarios.

2) In section 4.4.1 the advice to ask the patient to adapt their motor commands seems out of place. In my experience problems at this stage are usually hardware-related (socket fit, electrode placement) or software/programming-related.

We agree with you that at this point socket issues or problems with software settings might cause problems, and have added this in the manuscript. We sometimes experience that patients perform too strong contractions/do not relax when initially working with the prosthesis, which is what we meant with “adapt motor commands”. We have now explained this as well.

3) In section 5.1: is this the first multidisciplinary consultation the patient has after their initial consultation before surgery? I suspect that at the author's institution, the proximity of training facilities, the surgical unit, and laboratory facilities, may blur out the need for multidisciplinary sessions, as the surgeon may meet with the patients during their therapy sessions. In my institution, the therapists are several kilometres away in another part of town, and I think (the authors may well disagree and should then perhaps state so?) there will surely be a need for multidisciplinary or at least surgeon involvement between the initial preoperative consultation, and a point three months after discharge from rehabilitation.

Thank you for this very relevant point. We are indeed in the fortunate position to have the full team in close proximity, and to have a core team which works together closely. However, you are right that in a situation like yours planned multidisciplinary consultations are needed during the rehabilitation process. We have added this to the manuscript.

4) Considering that there are not a lot of these patients, and that they often come from far away,
a) do the authors have recommendations on which kinds of signal and/or prosthetic training could be performed at home. Do you provide EMG-biofeedback systems or even table-top prosthesis for the patient to take home with them? Or is the first hardware that the patient can bring home the complete prosthesis after fitting?

This is a very good point, and we dedicate a full paragraph to this in the revised discussion. In our experience, the early post-surgical interventions can be performed as home training and may be supported with video-calls if patients are coming from far away. We feel that the signal training should be started as an intense training week at the “TMR centre” at a time-point when we expect reinnervation of all muscles. In our experience a majority of patients learns a good signal separation in this time. Otherwise, we either recommend that they buy simple two channel sEMG biofeedback devices in their home country or provide them with a one (Myoboy). We think that more complex systems (or even a table-top prosthesis) are too costly as there is a risk of damage and they might overwhelm the patients with their options/settings.

b) During the COVID pandemic, there have been fast advances in the use of remote meetings and video-calls by some therapists. Does the authors' institution have any recommendations on remote solutions for the consultations/therapeutic training/follow-up visits?

As we are explaining in the revised discussion, we consider video-calls a good supplement in the rehabilitation of patients who cannot come to the clinic. We use them mostly to supervise home training and to support the patient when using the prosthesis at home. In our opinion, any solution that provides a stable video and audio connection while fulfilling all data protection requirements is fine. In Austria, this is e.g. room4physio. However, as data safety regulations differ between countries and the market for these solutions seems very dynamic, we prefer not to recommend any solution in the manuscript.

Reviewer #2:

Manuscript Summary:
This is a review of therapy approach to optimize prosthetic control after TMR.

Major Concerns:
No major concerns

Thank you for taking the time to review this manuscript, and for your feedback on how to further improve it.

Minor Concerns:
I would consider the below points to strengthen the manuscript.

1. The authors had excellent outcomes. Some of this is likely secondary to their extensive screening process and some is likely a result of selection bias as patients who received prosthetics were highly motivated. Possible limitation of the study.

We agree that the inclusion of highly motivated patients certainly helps to achieve the described outcomes. In the revised discussion, we describe this and add that including less compliant patients might result in reduced prosthetic function.

2. The authors should discuss whether / how they would modify their technique if TMR is done immediately at the time of a traumatic amputation as this is becoming more commonplace. Would they make any changes to post-operative therapy regimens?

Thank you for bringing up this relevant point that we are now discussing in the revised manuscript. We think that the psychological screening/support might be of higher importance due to the higher risk of developing PTSD etc shortly after amputation. Apart from this, we expect a quicker rehabilitation as the cortical representation of the lost arm should be better and as the patient is still used to bimanual activities.

3.Line 333. Did the five patients who were excluded because of cost of the fitting undergo TMR? If so do the authors believe that these patients should have been identified and excluded earlier based on their algorithm (link 114). Would they suggest any changes?

The five patients did indeed decide against a fitting after undergoing TMR. For three of them, the financial burden was the main issue for non-continuation with a fitting. These patients were confident that they would receive funding for their fitting when they approached us for surgery. It is indeed unfortunate that they were not excluded earlier. However, we decided that patients who make it probable or credible that they will have funding for a fitting, should not be excluded, even if the full funding is not available at the time of surgery. While we discuss consequence with these patients prior to surgery, we feel that the final decision should be up to them. As described in the original publication for the clinical study (*Salminger, S. et al. Outcomes, challenges and pitfalls after targeted muscle reinnervation in high level amputees. Is it worth the effort? Plast Reconstr Surg. 10.1097/PRS.0000000000006277, (2019)),* only about half of the patients approaching our centre who would fulfil the medical criteria for TMR receive the surgery due to financial concerns. We therefore feel that we are already having sufficiently strict inclusion criteria regarding funding.

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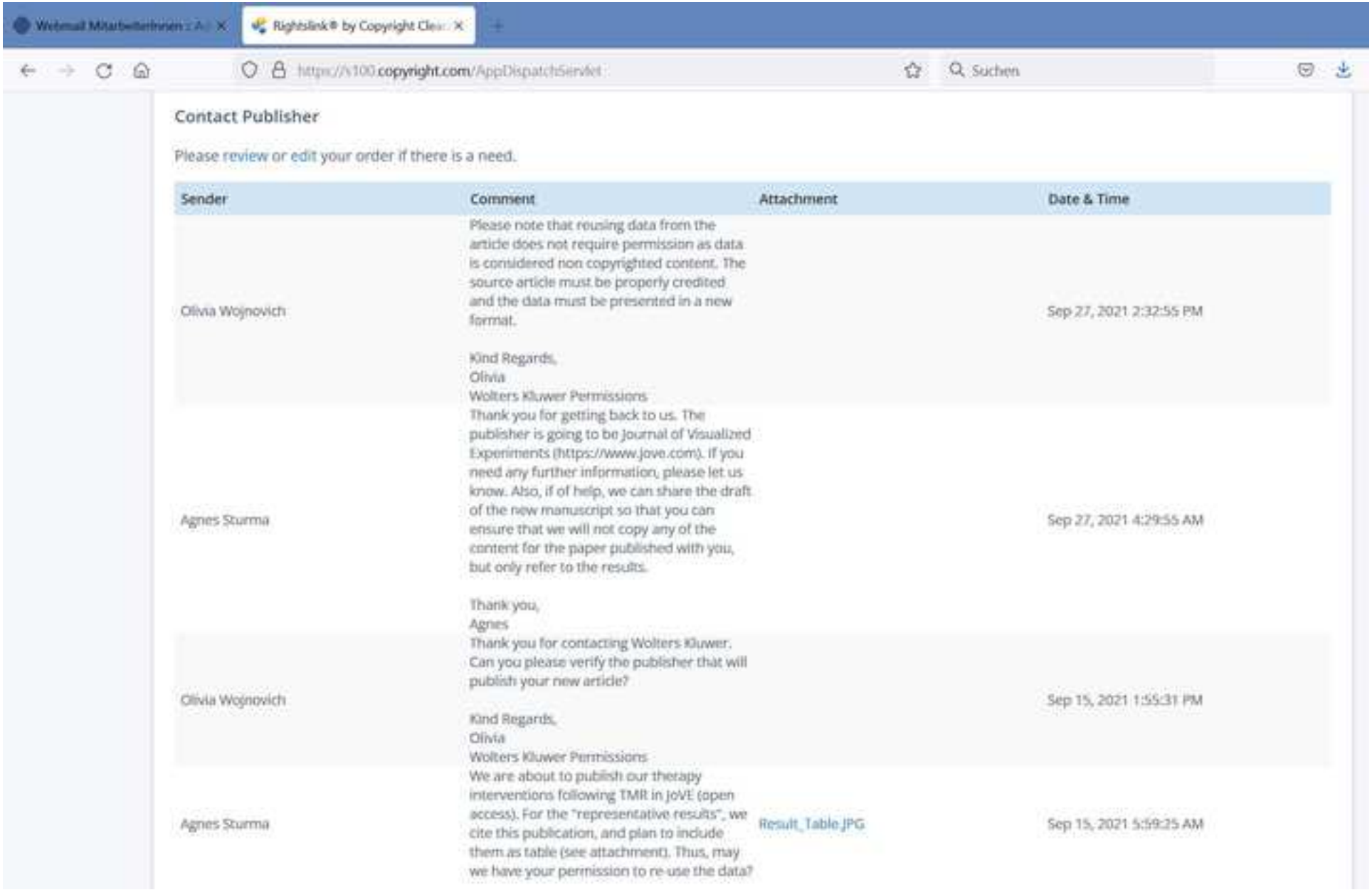

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Cambridge, MA 02140
tel. 617.945.9051
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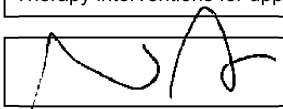
CORRESPONDING AUTHOR

Name:	Oskar C. Aszmann
Department:	Department of Plastic and Reconstructive Surgery
Institution:	Medical University of Vienna
Title:	Therapy interventions for upper limb amputees undergoing selective nerve transfers
Signature:	
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